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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JULY 1950

ORIGINAL ARTICLES

STUDIES ON THE USE OF AUREOMYCIN IN HEPATIC DISEASE*

I. AUREOMYCIN THERAPY IN ACUTE VIRAL HEPATITIS

By James M. Shaffer, M.D.

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Joseph Stokes, Jr., M.D.

and

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PHILADELPHIA, PENNSYLVANIA

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As a general introduction to the 4 Parts of this report, it should be stated that several difficulties are apparent in evaluating the possible effect of any therapeutic agent, such as an antibiotic, in viral hepatitis. Chief of these is the difficulty of making a diagnosis in a sufficiently early stage of the disease to permit therapeutic tests at a time when they might be the most critical. Another major difficulty is a variability in severity of signs and symptoms, certainly equal to that of any known infectious disease and greater than most.

Despite these and lesser difficulties, it appeared worth while to test the value of aureomycin in alternate cases of epidemic hepatitis as soon as they became available to the staffs at The Children's Hospital of Philadelphia and at the Hepatic and Metabolic Center, Valley Forge General Hospital. Suggestive evidence was soon obtained that the antibiotic apparently exerted little, if any, effect on the length or severity (except possibly in hepatic coma) of the acute symptoms, but that late manifestations of the disease might to some extent be controlled.

Upon this suggestive evidence from the acute epidemic cases, a tentative hypothesis for further studies was derived. This hypothesis was based upon the premise that liver injury from viral, nutritional, or other factors, may be accentuated by the passage of products of the intestinal flora or of the micro-

* This work was supported by the Commission on Liver Diseases of the Armed Forces Epidemiological Board, Preventive Medicine Division, Office of the Surgeon General, Washington, D. C.

örganisms themselves through the liver. Such products could include viral or bacterial metabolites and materials produced by bacterial action on intestinal contents.

It is, of course, also conceivable that microörganisms derived from elsewhere than the intestine might accentuate such liver injuries in certain cases, particularly if any synergism existed between virus and bacterium in liver disease.

Based upon this tentative hypothesis, 3 additional studies were initiated: 2, The possible protective effect of aureomycin by mouth on the hepatic necrosis in rats occurring on a diet in which yeast is the sole source of protein; 3, The treatment with aureomycin of hepatic coma, secondary to viral hepatitis, and to chronic liver disease, and 4, The treatment with aureomycin of all chronic liver disease in which no improvement had occurred over a period of several months. The 2d study has furnished some support, at least in these animals, to the hypothesis outlined, since in rats fed aureomycin in a diet containing no sulfhydryl amino acid or vitamin E, hepatic necrosis was prevented or significantly delayed, whereas the controls on the same deficient diet, lacking aureomycin, regularly succumbed to hepatic necrosis.

Method of Study. *Subjects.* The patients included in this study were divided into 3 groups by reason of age and location. The first group consisted of children from 3 to 13 years of age, inclusive, treated at the Children's Hospital of Philadelphia. The second group included adult males admitted to the Valley Forge General Hospital. The third group was equally divided between adult males and females who developed hepatitis at 2 institutions in New Jersey.

The patients were assigned to a treated or control group on an alternation basis, and cases were included only if therapy could be started within 7 days from the onset of jaundice. The treated and control groups were approximately equal in respect to average age and the number of each sex and race.

Aureomycin Treatment Schedule. Adults received 1 gm. of aureomycin orally every 6 hours for 10 days, except the first 4 (treated at the Army Hepatic and Metabolic Center, Valley Forge General Hospital), who received one half this dose, and 1 patient who had 4 gm. for only 6 days. The children were given comparable amounts based on 30 mg. per lb. per 24 hours in divided doses for 7 to 10 days.

Aureomycin was temporarily reduced or omitted in a few patients until nausea and vomiting subsided. It was not possible to determine to what extent aureomycin rather than the hepatitis was responsible for such symptoms in these patients. Milk, small feedings, or an aluminum hydroxide preparation given with each dose of the antibiotic often relieved the complaints.

Other Treatment. Additional treatment for all patients was as follows: 1, Bedrest was continued until jaundice subsided completely (toal serum bilirubin under 1 mg. per 100 ml.). Adult patients were kept in bed for at least 1 month; 2, High caloric, high protein, high carbohydrate diet was given; 3, Intravenous fluids (plasma and glucose in water or saline) were given to patients with persistent vomiting until the vomiting subsided. The few patients who received intravenous fluids were distributed equally in the treated and control groups; 4, Multi-vitamin supplements were given; 5, A gradual return to normal physical activity was arranged according to clinical improvement and in accordance with changing tests of liver function. Liver function studies were normal at the time of discharge except in a few patients with mildly positive serum flocculation tests.

Clinical and Laboratory Studies. All patients managed at The Children's Hospital and at Valley Forge were examined daily; those from the 2 isolated institutions were seen twice weekly.

Each patient had a blood count, urinalysis, and Wassermann test on admission. Blood counts and urinalyses were done weekly on all patients at the Valley Forge General Hospital. The aureomycin-treated group at Valley Forge received weekly determinations of prothrombin, bleeding, and clotting times. From a larger group of liver function studies done on most of the patients, the following were selected to measure the response to treatment:

Tests	*"Normal" Range*
A Total serum bilirubin	1.0 mg. per 100 ml. or less
B Thymol turbidity	3.0 units or less
C Thymol flocculation	Less than 1+
D Cephalin-cholesterol flocculation	Less than 1+ in 24 hours
E Urine bilirubin (Harrison spot)	Less than 1+

The limits of the so-called normal range are arbitrary and do not imply that results deviating slightly from these are necessarily abnormal. The onset of jaundice has been selected arbitrarily as the point from which the duration of abnormal hepatic function is measured in days. A plus sign after a figure on the charts indicates that this test was still positive when the patient was last observed. The length of follow-up on patients included in this report was 4 to 9 months; patients at the Hepatic and Metabolic Center are to be followed at 3 to 6 month intervals.

Results. There was no appreciable difference in the clinical or laboratory response between patients who received aureomycin and those who did not. The difference in the duration of positive liver function studies in the treated and control groups, as shown in Tables 1, 2 and 3, is not statistically significant. The thymol turbidity and flocculation tests returned to normal in the adult group at Valley Forge some-

TABLE 1.—DURATION IN DAYS OF ABNORMAL LIVER FUNCTION TESTS

GROUP I

Patient	*Age*	*Sex*	*Race*	*Bilirubinuria*	*Elevated Total Serum Bilirubin*	*Elevated Thymol Turbidity*	*Pos. Thymol Flocculation*	*Pos. Ceph. Chol. Floc.*
A. TREATED WITH AUREOMYCIN								
1	3	M	W	5	—	—	—	—
2	3	M	C	0	3	10	10	10
3	8	F	W	7	11	*10+	*10+	*10+
4	5	M	W	7	10	—	—	—
5	6	F	W	0	16	*33+	*33+	*33+
6	5	M	W	33	*46+	42	32	42
7	7	M	W	6	20	34	34	34
8	6	M	C	—	27	*27+	*27+	*27+
9	8	F	W	11	35	19	19	35
10	13	M	W	7	25	*25+	*25+	25
11	7	F	W	3	12	*12+	*12+	*12+
12	3	M	W	3	—	—	—	—
13	11	M	W	—	10	*11+	*11+	*11+
Aver.	7			7.5	20+	22+	21+	24+
B. CONTROLS								
1	12	F	W	13	—	—	—	—
2	6	M	W	5	7	—	—	* 5+
3	7	M	W	0	*10+	*10+	*10+	*10+
4	12	F	W	4	—	—	—	—
5	7	M	W	5	20	14	14	14
6	7	M	W	3	14	*14+	*14+	*14+
7	10	M	W	12	23	27	27	15
8	3	M	C	4	9	20	*20+	10
9	11	M	W	3	5	*26+	*16+	16
10	7	F	W	10	21	21	*21+	0
11	3	F	W	3	8	—	—	—
12	4	F	W	4	—	—	—	—
13	6	M	W	4	11	17	17	18
Aver.	7			5.4	13+	19+	19+	11+

* Indicates an abnormal test persisting at the time of the last determination.

TABLE 2.—DURATION IN DAYS OF ABNORMAL LIVER FUNCTION TESTS

GROUP II

Patient	Age	Sex	Race	Bilirubinuria	Elevated Total Serum Bilirubin	Elevated Thymol Turbidity	Pos. Thymol Flocculation	Pos. Ceph. Chol. Floc.
A. TREATED WITH AUREOMYCIN								
1	21	M	W	16	33	103	*103+	*103+
2	26	M	W	55	86	0	0	0
3	18	M	W	20	45	27	33	33
4	41	M	W	11	60	18	0	25
5	26	M	W	17	35	52	35	17
6	26	M	W	11	21	17	0	0
7	21	M	W	8	25	0	0	0
8	20	M	W	31	70	14	0	27
9	21	M	W	14	39	0	0	0
10	21	M	W	21	49	32	28	18
11	25	M	W	32	48	66	66	55
12	20	M	W	24	48	67	67	45
13	25	M	W	21	46	68	41	28
14	21	M	W	23	52	0	0	0
15	20	M	W	11	39	35	0	14
16	20	M	W	8	34	0	0	0
17	36	M	W	12	26	0	0	0
18	21	M	W	12	20	20	20	25
Aver.	24			19	43	29	22+	22+
B. CONTROLS								
1	22	M	W	14	35	70	70	48
2	19	M	W	30	42	66	*98+	51
3	21	M	W	14	70	103	103	78
4	31	M	W	17	55	*108+	0	24
5	20	M	W	16	26	0	0	0
6	31	M	W	17	30	0	0	0
7	38	M	W	19	54	25	26	34
8	38	M	W	22	71	*176+	176	162
9	24	M	W	30	67	0	0	0
10	25	M	W	38	83	48	41	38
11	21	M	W	21	49	0	0	0
12	28	M	W	12	45	82	0	0
13	24	M	W	32	64	78	0	53
14	30	M	W	7	25	14	18	18
15	21	M	W	15	49	65	65	41
16	30	M	C	12	29	40	0	15
17	30	M	W	15	47	19	0	26
18	18	M	W	31	54	25	25	25
Aver.	26			20	50	51+	35+	34

* Indicates an abnormal test persisting at the time of the last determination.

what sooner in those who had received the antibiotic, although this difference also is not statistically significant. The duration of positive liver function tests was greater in all adults than in children, in whom the illness was much milder.

Aureomycin caused only minor undesirable side effects in these patients with acute infectious hepatitis who received a 10 day course of therapy. In children, the antibiotic frequently appeared responsible for nausea and vomiting. The following complaints attributed to aureomycin were observed among adult patients: loose stools, especially during the first few days of therapy, anal itching and burning, and occasionally a metallic taste. No dermal sensitivity was observed in this group. No significant alterations in blood counts, urinalyses, or in pro-

TABLE 3.—DURATION IN DAYS OF ABNORMAL LIVER FUNCTION TESTS

GROUP III

Patient	*Age*	*Sex*	*Race*	*Bilirubinuria*	*Elevated Total Serum Bilirubin*	*Elevated Thymol Turbidity*	*Pos. Thymol Flocculation*	*Pos. Ceph. Chol. Floc.*
A. TREATED WITH AUREOMYCIN								
1	18	M	W	8	23	25	*25 +	23
2	22	M	W	13	22	*30 +	*30 +	30
3	29	M	W	13	16	*23 +	*23 +	23
4	28	F	W	9	10	*30 +	*30 +	22
5	20	F	W	10	10	*18 +	*18 +	18
6	21	F	W	15	15	39	40	39
Aver.	23			11	16	28 +	28 +	26
B. CONTROLS								
1	25	M	W	12	22	*23 +	*23 +	23
2	14	M	W	1	15	*23 +	*23 +	23
3	28	M	W	11	19	26	*26 +	25
4	28	F	W	14	10	*40 +	*40 +	19
5	19	F	W	*13 +	22	*24 +	*24 +	21
6	20	F	W	9	12	19	*24 +	11
Aver.	22			10 +	18	26 +	27 +	20

* Indicates an abnormal test persisting at the time of the last determination.

thrombin, bleeding, and clotting times, were observed.

Summary and Conclusions. 1. Aureomycin was administered orally in doses of 2 or 4 gm. daily for 6 or 10 days to 3 groups of patients (37 individuals in all) with acute viral hepatitis with jaundice. Control cases, 37, received the same routine management without aureomycin.

2. The duration of abnormal liver function was measured by an assemblage of hepatic function tests performed at frequent intervals.

3. Comparison of the 3 groups has shown no significant difference in the average duration of jaundice, bilirubinuria, or positive flocculation tests, or in the clinical picture of the acute and convalescent phase of the disease, between those receiving aureomycin and the controls.

4. The average duration of positive flocculation tests and elevated thymol turbidity was shorter in one treated group of adults than in the controls. Study of a larger series of cases will be necessary to evaluate this apparent difference.

STUDIES ON THE USE OF AUREOMYCIN IN HEPATIC DISEASE*
II. THE EFFECT OF AUREOMYCIN ON EXPERIMENTAL DIETARY HEPATIC NECROSIS**

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Acute hepatic necrosis occurring irregularly in rats kept on a diet low in casein[3,4] and with great regularity[7,8,9] on rations containing yeast as sole source of protein may be prevented either by the addition of sulfur-containing amino acids (cystine or methionine) to the basal diet, or equally well by supplements of vitamin E[1,4,5,6,9].§

It is difficult to reconcile pure deficiency as the possible cause of dietary hepatic necrosis with the interchangeability of such different substances chemically as the sulfur-containing amino acids and tocopherol in the prevention of hepatic necrosis. The assumption has been made[4] that this interchangeability of cystine (methionine) and tocopherol more probably results from an underlying detoxifying mechanism than from the supply of a deficient nutritional factor. Both vitamin E and the sulfur-containing amino acids are known detoxifying agents which may counteract the noxious effect of hepatotoxic and related substances. In the case of dietary hepatic necrosis such toxic substances may originate in the intermediary metabolism or under the influence of the intestinal flora, particularly in the large intestine.

The predominant occurrence of the pathologic changes in the left half of the liver of rats dying from dietary hepatic necrosis was first suggested by Himsworth[7] as being related to the dual blood supply of the liver. Blood supplying the right half of the liver through the portal circulation drains mainly from the small intestine whereas the left half of the liver receives its portal blood chiefly from the stomach, spleen and large intestine. Food constituents, such as sulfur-con-

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** Preliminary report was given by P. G. at the Fourth Conference on Biological Antioxidants, 1949, sponsored by the Josiah Macy, Jr., Foundation.

§ Under special experimental conditions only vitamin E proved to be effective in the prevention of acute diffuse hepatic necrosis[10,14].

taining amino acids and vitamin E when ingested are absorbed from the small intestine and may therefore exert their protective effect on the right half of the liver, as postulated by Himsworth[7]. On the other hand, if "toxic" substances are absorbed from the large intestine, perhaps as products of the intestinal flora, it is to be expected that the "left liver" would show more distinct pathologic changes than the right liver. Thus, toxic etiology would be consistent with the predominance of necrosis in the left half of the liver.

Parallel with these experimental studies clinical observations were carried out with respect to the possible effect of aureomycin on viral hepatitis. From these observations on hepatitis and on hepatic coma of varying etiology it became evident that aureomycin did not act on the hepatitis virus *per se* and the therapeutic results might have resulted from an indirect mechanism via an inhibitory effect on the intestinal flora. The assumption was made by one of us (J.S.) that an injured liver, such as one injured by hepatitis virus, is unable to cope with absorbed toxic metabolites of the intestinal flora, and that this increases the hepatic damage.

In the light of these considerations, based on clinical observations as well as on the interpretation of findings in dietary experimental hepatic necrosis, the question arose as to whether aureomycin might also be beneficial in rats kept on the basal necrogenic diet without supplements of protective substances, such as cystine or tocopherol.

Experiments. As in our previous experiments[1,6], the following "necrogenic" experimental diet was used: Yeast (British type of baker's yeast*) 18; corn starch, 79; salt mixture (USP II), 3. Peanut oil, 0.5 ml., and cod liver oil, 2 drops, were added to 8 gm. of the dry mixture just before feeding. Further, all animals received daily supplements of 20 micrograms of thiamine, 25 mcg. of riboflavin, 20 mcg. of pyridoxine, and 100 mcg. of calcium pantothenate dissolved together in 1 ml. of water. Rats were of the Sprague Dawley strain, males, with an average weight of 138 gm.

One sub-group of 20 rats with an average weight of 135 gm. received the basal experimental diet. A second sub-group of 22 rats with an average weight of 142 gm. was fed the same basal diet with a daily supplement of 0.1 gm. of aureomycin added to the diet-mixture. All rats were kept in single cages, with raised, wide-meshed screen bottoms. The daily food intake was measured.

Results. The results obtained clearly demonstrate (Fig. 1) that aureomycin exerted a statistically significant protective effect on rats maintained on the usual necrogenic yeast diet. At the end of 170 days, 18 of 20 animals in the control group not receiving aureomycin had died from acute massive hepatic necrosis, and death began to occur at 105 days. It is of interest and probably of significance that in the group of animals receiving aureomycin the protection exerted by aureomycin was mainly of a delaying nature. After 160 days, rats of the "aureomycin group" began to die of typical massive necrosis, recognizable grossly at autopsy, and confirmed by microscopic examination. Nevertheless, even at the termination of the experiment, after 200 days, the number of surviving rats was definitely higher in the group of animals receiving aureomycin than in the control group. In the control group only 2 rats survived the total length of the experimental period (200 days), while 11 rats of the original 22 in the aureomycin group were alive after 200 days. All surviving rats were killed at the end of the experiment and showed normal livers at autopsy. Further, it should be pointed out that in 8 out of

* "D.C.L. Vitamin B_1 yeast" from Distillers Corporation, Ltd., Glasgow C_4, Great Britain.

11 animals in the control group which died after 150 days or more of the experiment, the left lobe of the liver showed old scars, in addition to fresh necrotic lesions. Necrosis was present in all these 11 animals and not always restricted to the left lobe. No "scarring" was seen in any rats of the control group which died before the 150th experimental day or in any rats of the aureomycin group. "Scarring" indicates a previous attack of necrosis. Thus, it may be postulated that in the control group, a large number of rats must have recovered from necrosis of the liver some time in the early phase of the experiment and succumbed later to a recurrent attack of the same disease.

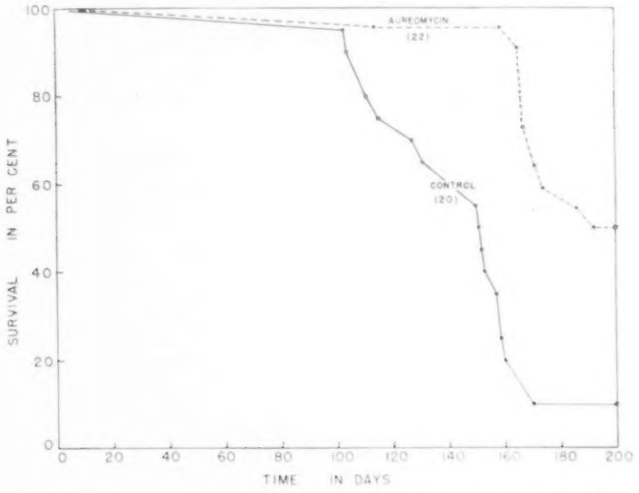

FIG. 1.—Survival rate of rats receiving the basal necrogenic yeast diet, with or without aureomycin. Figures in parentheses represent the initial number of animals in each group.

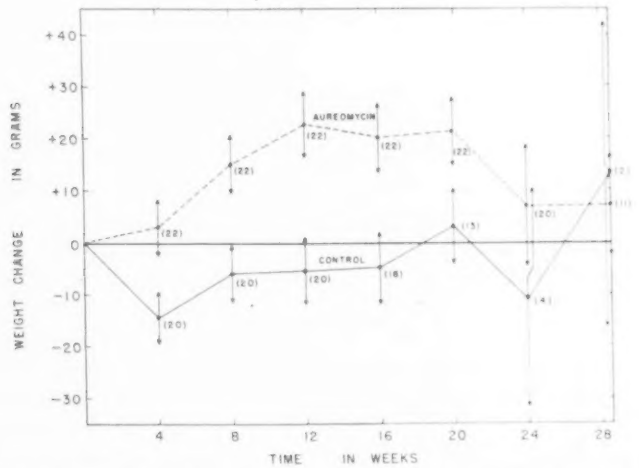

FIG. 2.—Weight changes throughout the experiment in the groups of animals with or without aureomycin. The figures in parentheses represent the number of rats in the respective groups at the indicated time.

Animals fed the basal diet without aureomycin showed a marked decline of the average weight curve during the first 4 weeks of the experimental period with consecutive slight increase and later stabilization of weight changes. In contrast, animals maintained on the basal diet and aureomycin exhibited a steadily rising average weight curve from the start up to the end of the 12th experimental week, followed by stable and later declining average weights toward the 24th experimental week (Fig. 2). The differences, as manifested by average weight changes in the 2 experimental groups of animals, were statistically significant up to the 20th experimental week. The small number of surviving rats in the control groups beyond the first 20 experimental weeks precludes a satisfactory statistical analysis for these later experimental periods.*

on the prevention of dietary hepatic necrosis is reminiscent of similar effects exerted by sulfur-containing amino acids or vitamin E. Aureomycin used for the present experiments was analyzed for sulfur and for vitamin E activity with completely negative results. Sulfur was determined chemically. Vitamin E activity was examined by the "hemolysis test"[6,13]. The red blood cells of rats kept on the basal yeast diet, washed and suspended in buffered saline solution, may be hemolyzed by minute amounts of dialuric acid, indicating vitamin E deficiency, at least with regard to the red blood cells. A supplement of aureomycin to the diet deficient in vitamin E was without any effect on this special fragility of the red blood cells, and, in consequence, on the underlying vitamin E deficiency.

Rats treated with aureomycin, re-

TABLE 1.—WEIGHT CHANGES COMPARED TO FOOD INTAKE.

Average Food Intake	*Weeks* 1–4	5–8	9–12	13–16	17–20	21–24	25–28
Control Group	7.5±0.16	7.8±0.17	7.4±0.23	7.6±0.13	8.0±0.13	7.5±0.14	8.0±0.20
Aureomycin	7.5±0.12	8.2±0.05	8.3±0.08	8.3±0.06	8.2±0.07	8.2±0.06	8.2±0.12

The average weight changes registered in the various 4 week periods may be compared with the corresponding food intakes during the same experimental periods.

It is apparent that in general rats of the aureomycin groups consumed slightly more food than the animals of the control group. However, it should be pointed out that during the first 8, and especially during the first 4 weeks, the differences in food intake cannot explain the markedly divergent weight curves observed in the 2 groups of animals.

The beneficial effect of aureomycin

gardless of whether they died from acute hepatic necrosis, or were killed in the absence of hepatic injury, at the end of the experiment, showed at autopsy a greatly dilated cecum and ascending colon. Similar findings were reported in germ-free animals by the group working at the University of Notre Dame[12]. Their occurrence under the influence of aureomycin may possibly be linked with the antibacterial effect of aureomycin on the intestinal flora.

Discussion. The prevention of massive hepatic necrosis in some rats, and the delayed production in others, un-

* Growth-promotion by aureomycin has also been observed in independent studies by E. L. R. Stokstad and T. H. Jukes (Personal communication, pub. in press).

der the influence of aureomycin, raise several problems. The paramount question pertains to the site of action of aureomycin. Does aureomycin exert a direct chemical effect on the liver, or does it act as an antibiotic agent, by suppressing an infectious process in the liver or by exerting its antibacterial effect on the intestinal flora?

In the past, intensive studies have revealed no indication of an underlying infection as the direct cause of so-called dietary hepatic necrosis[2,3,8]. Furthermore, it is difficult to reconcile the beneficial effect of sulfur-containing amino acids or vitamin E with an infectious etiology of massive hepatic necrosis. Thus, the choice seems to be between the direct metabolic effect of aureomycin on the liver and its antibiotic effect on the intestinal flora. Circumstantial evidence seems to favor the latter mechanism. It is a well established fact that aureomycin inhibits the intestinal flora, in particular the coliform organisms[14]. The greatly distended cecum and colon in the animals treated with aureomycin present a parallel picture to that seen in animals[12] free of all microorganisms.

The fact that the protective effect of aureomycin on experimental hepatic necrosis appears to be not as permanent as that of the sulfur-containing amino acids or of vitamin E tallies especially well with the assumption that it is mediated through the intestinal flora. If aureomycin acts through suppression of the intestinal flora, in particular of the coliform organisms, and by this action prevents the formation of bacterial metabolites, with which the liver in the absence of vitamin E or of sulfur-containing amino acids is unable to cope, it is to be expected that such effect will slowly wear off and then organisms may appear in the intestinal flora which are resistant to aureomycin.

If the role of aureomycin is not specific, other satisfactory methods leading to similar changes in the intestinal flora should be equally effective.

The possibility exists that aureomycin may contain some specific liver protecting compound, different from sulfur-containing amino acids or vitamin E. The yeast ration is free from vitamin B_{12}. In view of this fact the effect of vitamin B_{12} (in doses of 1 γ per day) in the prevention of hepatic necrosis was investigated, with negative result[5].

Summary. Aureomycin when added to a necrogenic yeast diet, has a significant beneficial effect on the prevention of experimental hepatic necrosis in rats. The assumption is made that aureomycin might act through the suppression of the intestinal flora. In the absence of sulfur-containing amino acids or of vitamin E as detoxifying agents, the products of uninhibited intestinal flora may be responsible for experimental acute dietary hepatic necrosis.

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HYDROPS OF THE FETUS: A MANIFESTATION OF SHOCK*

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A recent study of autopsy findings in infants suggested that shock, usually caused by or associated with anoxia, frequently occurs in the newborn[7]. With this in mind, the question arose how shock might manifest itself under the conditions peculiar to intrauterine life. One manner in which the existence of the placental circulation might influence the course of events, suggested itself as follows: it has been accepted by most investigators that in shock the capillary walls are damaged and their permeability is increased. This results in loss of fluid from the circulating blood to the tissue spaces, with hemoconcentration and edema[17]. The degree of edema thus produced, in the adult, is limited by the amount of fluid which can leave the blood stream. In the case of the fetus, however, any fluid lost from the blood stream may be replaced immediately by the practically unlimited reservoir of fluid of the maternal organism, available by way of the placenta. Consequently, much more fluid can leave the fetal circulation and lead to excessive edema or hydrops. The following experiments were designed to test this hypothesis.

Experiments. A method was sought by which shock could be produced in the fetus in utero. Moon[17] used the intraperitoneal administration of muscle pulp as the method of choice in his investigation of the pathology of experimental shock in animals. This technique was adapted for the purpose of the present problem. Muscle tissue from a freshly killed guinea pig was finely ground in a blendor with 3 times its weight of saline. A small amount of charcoal was added so that the site of injection might be seen subsequently at autopsy. A pregnant guinea pig was anesthetized with ether or chloroform, and a median laparotomy was performed. The uterus was exposed, and the abdomen of a fetus located by inspection or palpation. The muscle pulp preparation, to the amount of 0.2 cc. per 10 gm. of estimated weight of the fetus, was then injected intraperitoneally into the fetus through the intact uterine wall. This corresponds to 5 gm. of muscle tissue per kg. of fetal body weight. Other fetuses of the same litter served as controls, being injected either with the same volume of saline, with or without charcoal, or left untouched. The incision was then closed and the animal returned to its cage. The duration of the experiment was limited by the fact that abortion usually occurred from 12 to 24 hours later. Only in 3 instances was the animal killed after 24 hours without having aborted. All fetuses were weighed and photographed, and then fixed in formalin. The weight could not be used as a measure of their edema because of its wide variation among litter mates. Sections of the heart, lung, liver, kidney, adrenal, and in some instances skin and placenta were prepared for microscopic examination. These showed no significant changes and will not be described further.

Results. Several experiments were rendered useless by one of the following factors: One was the attempt of

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the mother to eat and thus mutilate the aborted fetuses if they were not immediately removed from the cage. The other factor was the advanced age of several litters. These fetuses received relatively less muscle pulp since not more than 1 cc. was ever given. They were aborted soon after the injection and their relatively dense tissues and well developed fur made the recognition of moderate edema impossible. Thus, fetuses weighing 60 gm. or more proved to be unsuitable. Furthermore, they are not strictly comparable with human or most other mammalian fetuses, being considerably more mature.

The suitable experiments are listed in Table I. Ten litters yielded 17 fetuses injected with muscle pulp and 14 controls. All fetuses injected intraperitoneally showed definite edema (Figs. 1 to 3). Their skin was tense and shiny and did not show the usual wrinkles (Figs. 1 and 2). Edema was most conspicuous in the loose skin of the neck region (Figs. 1 and 3). In 3 instances in which injection inadvertently had been made intramuscularly, the result was inconclusive. In one instance (Litter 7) there was no appreciable edema. In the other two instances (Litters 4 and 10) intramuscular injection produced less edema than did intraperitoneal administration in litter mates (Fig. 3). In these 3 instances the injected material accumulated as a solid mass in a small area, and probably was not as readily absorbed as that reaching the peritoneal cavity. None of the injected or uninjected controls were edematous.

Discussion. Inasmuch as the experiments were limited to a period of 24 hours or less, the results are regarded as significant and support the present hypothesis that severe edema of the fetus may be a manifestation of shock. These experiments are not intended to prove that this is true in every instance of hydrops or neonatal edema.

Since most of the cases of hydrops of the fetus are due to isoimmunization of the mother by fetal blood group factors, the cause—if not the mechanism—in these instances is now generally known. Most of the varied theories concerning the nature of hydrops were proposed before this knowledge was available. At that time, various authors proposed or supported, among others, the following theories of the cause of hydrops: fetal or maternal disease of

TABLE 1.—SUMMARY OF EXPERIMENTS

		*Muscle pulp and Charcoal**		*Controls**		
Litter	*Approximate weight of fetuses (grams)*	*intra-peritoneal*	*intra-muscular*	*saline and charcoal*	*saline*	*not injected*
1	18	1++	0	0	0	3−
2	12	2+++	0	0	0	2−
3	54	1++	0	0	0	0
4	33	1++	1+	0	1−	0
5	23	2++	0	0	1−	0
6	20	2++	0	0	2−	0
7	29	1++	1−	0	2−	0
8	42	2+++	0	1−	0	0
9	45	1++	0	1−	0	0
10	8	1+++	1+	0	1−	0
Total		14	3	2	7	5

*These columns show the number of fetuses treated. Beside the figure + and − signs indicate the degree of edema.

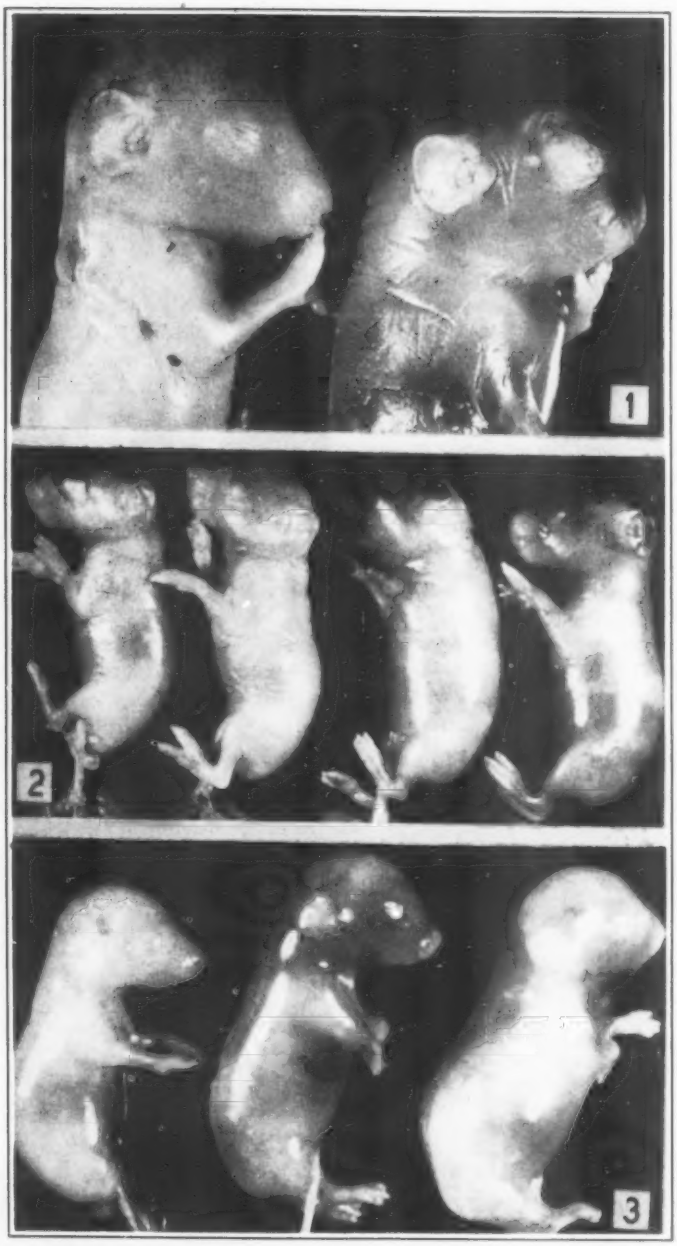

FIG. 1. The effect of injected muscle pulp on guinea pig embryos. An uninjected control (left) and an intraperitoneally injected fetus (right) from Litter 2.

FIG. 2. Litter 6. The 2 embryos to the left were injected with saline, the 2 to the right with muscle pulp, all intraperitoneally.

FIG. 3. Litter 10. The control injected with saline on the left. On the right after intraperitoneal injection with muscle pulp. In the middle, after inadvertent injection of muscle pulp intramuscularly. All embryos which received muscle pulp, are edematous. In Litter 10, the one injected intramuscularly is less edematous than that injected intraperitoneally.

various kinds[3,16,19,23] including renal disease; hormonal inbalance related to follicular hormone[23], gonadotropic hormone[9,26], hyperinsulinism[15], or malformations of the pituitary[13,14]; the action of toxic substances including histamine on fetal capillaries[2,3,4,5,11,16,25]; a primary abnormality of the placenta producing anoxia or increased resistance in its circulation[3,8,10,19]; anoxia due to anemia[6] or from other causes[8]; angioneurotic edema[3]; a functional immaturity of the fetal organism[13]; hypoproteinemia due to liver damage[6,12]; or various malformations which are known to be occasionally associated with hydrops[3,8,16,19,20]. Anaphylaxis was suggested by Darrow[5] before the occurrence of isoimmunization was known. Of particular interest in connection with our present theory are the suggestions that anoxia and various poisons which also damage the capillaries, are responsible for hydrops. Their action may be similar to that produced in our experimental animals by muscle pulp. Busch[2] specifically mentioned that histamine, which he thought to be the cause of hydrops, is a shock poison.

At present it is known that the majority of cases of hydrops occur with isoimmunization, and that a smaller group exists in which no history of blood group incompatibility between mother and fetus can be demonstrated. The latter group is characterized by the absence of extramedullary areas of erythropoiesis or an enlarged spleen[1,18]. No explanation has been offered for this group. In the light of the present experimental results one may interpret the first-mentioned group as due to a reaction similar to anaphylactic shock, and the second group as comprising cases in which shock occurred due to miscellaneous causes. In addition to hydrops proper, edema is often found in infants with erythroblastosis. The success of Jacobi, Litvak and Gruber[12] in treating this edema with serum albumin may be due to the control of shock. To these cases of outright hydrops and edematous erythroblastotics might be added a large number of newborn infants with marked edema which is not sufficiently conspicuous to be called hydrops. These edematous infants constitute 2 types, namely prematures, and infants born near term who are in poor condition and usually asphyxiated. Edema of prematures has been studied by Smith and associates[21,22] and appears to be due to inadequate regulation of proteins in the blood, and electrolytes in the body fluids. This is not related to the mechanism operating in shock, but the two may be superimposed. It is of interest in this connection that the smallest of our experimental fetuses had the most conspicuous edema (Fig. 3).

Asphyxiated infants are often unduly edematous, and it is conceivable that some of the instances of non-erythroblastotic hydrops owe their origin to prolonged intrauterine anoxia. This cannot be proved at the present time. The close relationship of anoxia and shock has been stressed with regard to man and animals in general[17] and newborn infants in particular[7].

Since it is extremely difficult to recognize shock in a newborn infant, the presence of marked edema may be one of a few suggestive signs. It should be kept in mind that owing to the peculiar circumstances of intrauterine life the excess of tissue fluid may be considerably greater in those instances than in adults who are in shock. This means that edematous newborn infants are particularly in need of substances which will remain in the circulation and perhaps even draw fluid from the tissue spaces. The more readily diffusible agents might themselves reach the tissue fluids and thereby help increase the edema. On this basis it is suggested that blood or blood fractions, or col-

loidal substitutes be given intravenously rather than salt solutions. It remains to be seen whether this knowledge will be beneficial in the treatment of an occasional case of hydrops born alive.

Conclusions. The present experiments, in which a standard method for the experimental production of shock was adapted for guinea pig fetuses, suggest that hydrops of the fetus is a manifestation of shock. The presumptive mechanism is discussed.

It is assumed that in man fetal shock, caused by isoimmunization of the mother and leading to hydrops or to less conspicuous edema is most commonly due to a reaction similar to anaphylactic shock. Other instances are probably due to various other agents producing shock, among them anoxia. This does not exclude the existence of a third group in which factors unrelated to shock, *e.g.*, malformations of the circulatory system, produce hydrops.

Suggestions for the treatment of edema of the newborn, and perhaps hydrops, are made on the basis of the present hypothesis.

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THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA WITH LARGE DOSES OF REPOSITORY PENICILLIN COMPARED WITH LOWER DOSES OF PENICILLIN: A STUDY OF 686 PATIENTS

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Although the efficacy of penicillin in the pneumonias caused by pneumococci is a well-established fact, there is no unanimity of opinion regarding the optimal dose which should be employed. Tillett and his associates[12] recommended frequent intramuscular injections omitting the night doses. Other early investigators[3,8,9] used repeated intramuscular injections throughout the entire 24-hour period. Later, penicillin was given orally although still at 3-hour intervals[2,4,6]. Recently, comparable results were obtained when 1 or 2 daily injections of aqueous penicillin were given[10,13,14]. Since the minimum concentrations of penicillin in the blood following the injections of 300,000 units of penicillin in oil and beeswax (POB) or procaine penicillin in oil (PPO) once a day are at least as good as those obtained with total daily doses of 300,000 units of aqueous penicillin regardless of the intervals at which the injections are given, repository injections of POB or PPO are now used extensively in the treatment of this disease[1,11]. Because a certain proportion of the patients with pneumococcic pneumonia treated by any of the aforementioned methods still die, we decided to try large doses of the repository preparation.

Material. Accordingly, we administered 600,000 units of penicillin in oil and beeswax twice a day to 238 patients, and 600,000 units of procaine penicillin in oil twice a day to 45 patients, with typed pneumococcic pneumonia. In the present paper, the results of treatment in these 283 patients (designated as the "large-dose group") are compared with the results obtained in 403 patients treated by us with other dosage forms of penicillin which produce lower blood concentrations (designated as the "small-dose group"). Among the latter, 236 were treated with intramuscular injections of penicillin at 3-hour intervals. In most cases, each dose was 15,000 units, but in occasional instances, it was 25,000, 50,000, or 100,000 units. Oral penicillin was given to 99 patients in doses of 80,000 or 100,000 units every 3 hours. Sixty-eight patients were given 300,000 units of procaine penicillin in oil with aluminum monostearate intramuscularly. Four of these patients received 2 injections 2 or 3 days apart. The remainder were given a single dose.

At least 1 specimen of sputum and blood was obtained from each patient for culture and typing. One or more roentgenograms of the chest were taken. If, upon the basis of the history, physical examination, and roentgenograms, the patient was thought to have pneumonia and a type of pneumococcus was

obtained from the sputum or blood, the patient was included among the patients herein reported.

The patients in the large-dose group were treated in the past 2 years, whereas those in the small-dose group were treated over the past 4 years. Other than this, no selection was practiced. The patients on an entire ward were given one or the other preparation of penicillin for several months without any alteration.

Results. In Table 1 are presented the results of treatment according to the type of pneumococcus and the presence of bacteremia. It will be seen that the proportion of patients affected by each type of pneumococcus was approximately the same in each of the 2 treatment groups. The case fatality rates in the 2 groups (5% in the large-dose, repository penicillin group and 5.4% among the patients treated with smaller doses of penicillin) were practically identical.

Bacteremia was present in 46 patients (16%) in the large-dose group and in 59 patients (14%) in the small-dose group. The fatality rates for the bacteremic patients in the 2 groups were very similar (13% and 10.2%).

The distribution of the patients in the 2 groups according to age (Table 2) was quite similar. Forty-seven per cent of the patients in the large-dose group were over 40 years of age and the fatality rate in this group was 8%. In the small-dose group 43% of the patients were over 40 years of age. The fatality rate in this group was 10%.

TABLE 1.—RESULTS OF TREATMENT OF PNEUMOCOCCIC PNEUMONIA ACCORDING TO TYPE OF PNEUMOCOCCUS

	Patients Treated with Large Doses of Repository Penicillin (POB & PPO)				*Patients Treated with Smaller Doses of Penicillin*			
	All Patients		*Bacteremic Patients*		*All Patients*		*Bacteremic Patients*	
Type of Pneumococcus	*No.*	*Died*	*No.*	*Died*	*No.*	*Died*	*No.*	*Died*
I	53	1	15	1	50	4	13	3
II	19	0	3	0	34	0	3	0
III	23	1	3	0	40	3	3	2
IV	26	1	2	0	23	0	7	0
V	4	0	0	0	6	0	1	0
VI	9	2	0	0	14	1	0	0
VII	17	1	3	1	53	1	12	0
VIII	23	3	8	3	23	1	4	0
Higher Types	109	5	12	1	160	12	16	1
All Types	283	14 (5.0%)	46	6 (13.0%)	403	22 (5.4%)	59	6 (10.2%)

The incidence of diseases associated with the pneumonia was approximately the same in the 2 treatment groups (Table 3). Death occurred as frequently among the patients in the large-dose group with complicating diseases as in the small-dose group.

The complications arising from the pneumonia are shown in Table 4. They were present to approximately the same degree in both groups. Death occurred in 1 patient with empyema in the "small-dose group" and in 1 patient

TABLE 2.—RESULTS OF TREATMENT OF PNEUMOCOCCIC PNEUMONIA ACCORDING TO AGE OF PATIENTS

	Patients Treated with Large Doses of Repository Penicillin (POB & PPO)		*Patients Treated with Smaller Doses of Penicillin*	
Age	*No. of Patients*	*No. Died*	*No. of Patients*	*No. Died*
Under 21	21	1	31	0
21–30	59	1	84	0
31–40	65	2	110	4
41–50	65	3	91	2
51–60	30	3	34	5
61–70	25	3	27	6
Over 70	13	1	23	5
Age unknown	5	0	3	0
Totals	283	14 (5.0%)	403	22 (5.4%)

TABLE 3.—DISEASES ASSOCIATED WITH PNEUMOCOCCIC PNEUMONIA AND THE RESULTS OF TREATMENT WITH PENICILLIN

	Patients Treated with Large Doses of Repository Penicillin (POB & PPO)		*Patients Treated with Smaller Doses of Penicillin*	
Associated Disease	*No. of Patients*	*No. Died*	*No. of Patients*	*No. Died*
Acute Alcoholism	22	3	32	1
Heart Disease*	15	4	13	7
Pregnancy	5	0	3	0
Bronchial Asthma	6	0	6	0
Hemiplegia	3	3	4	2
Pulmonary Tuberculosis	2	0	0	0
Bronchiectasis & Purulent Bronchitis	2	0	7	1
Diabetes Mellitus	2	0	5	2
Cirrhosis	2	1	3	0
Uremia	2	1	2	1
Congestive Heart Failure and Uremia	0	0	1	1
Totals	61	12 (20%)	76	15 (20%)

* Congestive Heart Failure or Auricular Fibrillation

TABLE 4.—COMPLICATIONS OF PNEUMOCOCCIC PNEUMONIA AND THE RESULTS OF TREATMENT WITH PENICILLIN

	Patients Treated with Large Doses of Repository Penicillin (POB & PPO)		*Patients Treated with Smaller Doses of Penicillin*	
Complications	*No. of Patients*	*No. Died*	*No. of Patients*	*No. Died*
Delayed Resolution	10	0	17	0
Pleural Effusion	5	1	6	0
Empyema	2	1	3	1
Spread to Another Lobe	1	0	0	0
Totals	18	2	26	1

with empyema and 1 patient with pleural effusion in the "large-dose group".

Discussion. When an effective therapeutic agent such as penicillin is available for the treatment of a disease as common as pneumococcic pneumonia, it becomes important to find out whether any dosage regimen will cause a further depression of the case-fatality rate below that already achieved with the doses routinely used. This is what we have attempted to do by treating 283 patients with 600,000 units of repository penicillin at 12-hour intervals. The fatality rate was almost the same as that obtained by us in patients treated with the more common penicillin dosage-regimens and the difference observed was not statistically significant.

In the search for an explanation of these unexpected findings, 2 possibilities appear likely. The most obvious explanation is that we have lowered the case fatality rate in pneumococcic pneumonia to an irreducible minimum beyond which it cannot go because of factors upon which the antibiotics cannot operate. Among the 14 patients who died after treatment with 600,000 units of repository penicillin at 12 hour intervals, 10 were over 40 years of age. Among these, 2 were admitted with acute alcoholism and pneumonia, 3 had hemiplegia and developed pneumonia as a complication, 2 had heart disease, 1 had cirrhosis of the liver, and 1 had prostatic hypertrophy, renal lithiasis and uremia. The 1 patient without an associated disease was a 42 year old colored woman who was admitted on the 7th day of the disease and who had pneumococcic arthritis as well as pneumonia on admission.

Among the 4 patients who were below 41 years of age, 1 was admitted with acute alcoholism and pneumonia, 1 had rheumatic heart disease upon which a bacterial endocarditis had been engrafted before admission, and 1 had pneumococci endocarditis, arthritis, and meningitis on admission. The 4th patient, who had no associated disease, was admitted moribund and died a few hours after a single dose of 600,000 units of POB.

Among the patients in the small-dose series who were 41 years of age and over and who died, 7 had congestive heart failure, 2 had hemiplegia and 1 each had acute alcoholism, essential hypertension, uremia and purulent bronchitis with lung abscess. Four patients died within 24 hours after the first dose of penicillin had been administered. Of the remaining 2 patients, 1 was 80 years old and the other was a 63 year old man with hypertension and diabetes mellitus.

Four patients died among the patients under 41 years of age in the small-dose group. One had congestive heart failure and chronic glomerulonephritis with uremia. One had diabetic acidosis. The 2 remaining patients died 8 and 15 hours after the first dose of penicillin was administered.

It may be of significance that 7 patients in the low-dose group died within 24 hours of admission, whereas only one patient in the repository penicillin group died during this period, although this difference may have been due merely to the fact that a larger number of moribund patients were included in the low-dose group. The question under consideration is whether any of the patients who died could have been saved by the employment of any dose of penicillin no matter how large. Or even if an increased dose of penicillin would have resulted in 1 or 2 fewer deaths, the difference could not be demonstrated even by the finest of statistical methods unless a much larger number of patients had been included in each series.

TABLE 5.—ANALYSIS OF CASES IN WHICH DEATH OCCURRED

	High-Dose Repository Penicillin Group		*Low-Dose Penicillin Group*	
Associated Diseases	*Patients under 41 years*	*Patients 41 yrs. & over*	*Patients under 41 years*	*Patients 41 yrs. & over*
Acute Alcoholism	1	2	—	1
Hemiplegia	—	3	—	2
Heart Disease	1	2	—	7
Cirrhosis of the Liver	—	1	—	—
Uremia	—	1	1	1
Essential Hypertension	—	—	—	1
Diabetic Acidosis	—	—	1	—
Purulent Bronchitis and Lung Abscess	—	—	—	1
Complications of Pneumonia Present on Admission	1	1	—	—
Died within 24 hours	1	—	2	5
Others	—	—	—	1
Totals (Omitting duplications)	4	10	4	18

Another possible explanation of the results obtained, concerning which it is interesting to speculate, is that the large doses of repository penicillin which we used, while assuring minimal penicillin concentrations, in practically every case, of 0.08 unit per cc.[7], actually did not produce very high peak concentrations such as would have been attained with 1,000,000 units of penicillin, for instance[5]. There are at present a number of proponents of the theory that high-peak concentrations of penicillin in the blood are more important than constant levels. If this theory is entertained, it would seem reasonable to try large doses of aqueous penicillin at infrequent intervals in pneumococcic pneumonia to determine whether the fatality rate could be depressed below 5%.

Summary and Conclusion. 1. We have treated 686 patients with typed pneumococcic pneumonia with penicillin, among whom 36 (5.2%) died.

2. The case fatality rate among 283 patients treated with 600,000 units of penicillin in oil and beeswax or 600,000 units of procaine penicillin in oil twice a day was 5%, as compared with a case fatality rate of 5.4% among 403 patients to whom penicillin was administered intramuscularly or orally in doses which produced lower average blood concentrations.

The fatality rates in bacteremic patients, in patients with complicating diseases, and among patients in the different age groups were comparable for the 2 series.

3. It is concluded that the administration of 600,000 units of repository penicillin twice a day in pneumococcic pneumonia yields results practically identical to the more commonly employed dosage forms.

We wish to thank Drs. Jay A. Robinson, William W. Zeller, Thomas E. Stone, and Walter Kurland for assistance in the clinical management of these patients.

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CLINICAL OBSERVATIONS ON TOLSEROL IN HANDLING ANXIETY TENSION STATES

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The appearance of any chemical compound on the medical horizon which might in any way bring about relief to the many sufferers of the common symptom, "anxiety", is of more than passing interest to the physician. Within recent months the reports from such investigators as Gammon and Churchill[3], Schlesinger, Drew and Wood[7], Schlesinger[6], Hunter and Waterfall[4], as well as the older investigations of Berger[2], Bradley[1], Stephen and Chandy[9], Schlon and Unna[8] and others on the compound 3-ortho-toloxy-1,2-propanediol ("Tolserol")* has led many people to the fascinating idea that there may be a new approach to the treatment of certain disabilities of the neuro-muscular apparatus giving anxiety as at least one of its symptoms.

We have long been concerned with the problem of anxiety, both from the research and treatment points of view. Anxiety has been defined as an unpleasant emotion generated as the personality is threatened by certain influences from within or without the individual. Anxiety as a symptom and an existing unpleasant emotion has been much studied from all conceivable angles by innumerable individuals. It has interested us that certain individuals such as Jacobson[5] have stated that all too often the student of anxiety has heeded what the patient was anxious or concerned about but failed to recognize the physiologic processes that might be taking place. We have tried especially to study the underlying physiologic processes occurring in any given state in anxiety and have come to the conclusion that, as such, anxiety is the emotional expression of a physiologic state in which the body, as a whole, is preparing itself to combat any known threat to its integrity. It is our further opinion that this particular state of preparation is manifest by more than just anxiety, but includes evidence of preparation in the entire neuromuscular set-up, bringing about what is commonly called "Neuromuscular hypertension", in the words of Jacobson[5].

We have come to believe, along with many others, that anxiety is one of the symptoms of a generalized state of neuromuscular hypertension which has been previously conditioned into the behavior of an individual by certain influences in that individual's earlier

* The drug used in this study was supplied by E. R. Squibb & Son under the brand name of Tolserol.

or pre-existing environment. Along with Jacobson[5] and others, we have come to the conclusion that neuromuscular hypertension, or as the expression more commonly exists, "anxiety tension states", are extremely common and, contrary to popular concept, exist largely in healthy, vigorous, able and capable individuals who are successful in the professions, the skilled type of vocations, people who are highly organized and often are successfully carrying out business ventures. Believing as we do that these individuals are conditioned into their existing state of anxiety, we have interested ourselves in those types of treatment which would allow us to reëducate or retrain this individual in a relatively short period of time to a physiologic state which would allow him to live comfortably, easily and without tension as such. In our treatment program, which has gradually evolved over a period of some 15 years, it was natural that we should include modifications of Jacobson's[5] technique of relaxation.

Therefore, as the various reports began to appear about the ability of the compound Tolserol to produce a state described by several authors as a complete state of "relaxation", "euphoria", "freedom from nervousness" or "tension", we decided to give varying amounts of Tolserol, during the course of a treatment program.

The majority of our patients were adults between 20 and 50. They were all individuals seen in private practice, all but a very few were active, working or quite busily engaged in keeping house, running a business or practicing professional activities. They were people referred for psychiatric treatment of various types of anxiety states by internists or diagnosticians who had adequately or completely ruled out any organic or physical basis for any existing state of anxiety. These people further were typical examples of anxiety tension states, having the characteristic hyper-activity or over-excitability of the autonomic or vegetative nervous system. They had, besides the dry mouth, occipital or pre-frontal headache, dilated pupils, cold perspiring hands and feet, gastro-intestinal distress, vascular hypertension, irritable skin, and the like, and the intense mood of anxiety or the marked fatigue that so frequently follows a prolonged period of chronic hypertension or acute anxiety. Some of them had also varying degrees of moodiness, irritability, "blueness" or depression which is also seen in some chronic hypertensive states. For want of a better classification, we have simply listed our cases "acute tension states", "habitual tension states" or "anxiety states", "tension depressions". We saw and included in our reports a few tension depression states which were in the climacteric age, and we termed these involutional or menopausal depressions, rather than tension depressions. This was done simply to keep in general agreement with others. These people, then, were healthy, hard-working, intelligent, conscientious individuals, satisfying almost anyone's diagnostic criterion for varying types of anxiety tension states.

Our approach to studying these people was to select rather carefully from the individuals we saw in private practice those whom we felt were absolutely free from any psychiatric or physical problem except true anxiety patterns. These individuals we knew very well from previous contact. They were people whom we were seeing at least 5 or 6 times a week, and in whom we had sufficient confidence to trust their using the drug by our direction, who could report to us clearly the reactions they received from the drug and who could be adequately handled without the element of suggestion entering into

their reaction in any way. Our seeing them daily and giving them only an amount to last them 24 hours gave us further assurance that only clear reactions from the drug were reported by us or to us. We first selected a small group to whom we gave varying amounts of the drug daily, and kept them in the office for varying lengths of time so that we could not only hear from the patients what they felt, but could observe as much as possible what occurred in each individual. When we found what range of drug seemed to work best, we then selected a larger group of people to whom we gave this range of drug over a period of time, noted reactions that took place, varying the amounts given as seemed necessary to produce the response we wanted. When this group of people had been completed, we then gave the compound to a much larger group of individuals, watching them a little less carefully, allowing them a little more liberty in making use of the drug, asking them to report various reactions which took place. We have in the past 9 months given the drug to approximately 500 patients. Of these many have been seen recently but are not included in this report. Here we are reporting only the observations and findings in a group of 124 individuals, the oldest being 59, the youngest 21, which have been carefully studied and watched over a period of time.

Observations. See also Tables 1, 2 and 3. Within 20 to 35 minutes after taking the adequate dosage, the individual has a very pleasant feeling of relaxation. This was described by the majority as "I have a feeling that for the first time I can let go." It was distinctly different from any feeling they had had previously, regardless of the use of any chemical agent. Certainly it was distinctly different from any feeling due to sedation. A few of them said that they felt, "like I had had an extra high-ball". There was the typical feeling of warmth, the circumoral numbness, or numbness all over, a feeling of "pins and needles". Some of them had blurred vision, some euphoria. Very few of them had a feeling of drowsiness or muscular incoordination. As is reported, a few, but very few, had a feeling of nausea or gastro-intestinal distress. A few who had had severe muscular cramps or spasms, or aches and pains, related to increased muscular activity had a dramatic release from these symptoms. In all except a very few, there was a dramatic and most satisfactory termination of the feeling of anxiety.

We emphasize that we did not in any case use the drug to create a prolonged period of relief, such as is commonly done with sedatives, but have used Tolserol in every instance to promote one satisfactorily comfortable interval of relaxation during a 24 hour period. In very few instances did this exist for longer than 2 or 3 hours. In the majority of instances following a psychotherapeutic interview, the patient would have an interval to go through the supervised learning of relaxation. Either prior to, during, or immediately following this particular period, the patient would be given the drug so that he could experience, with the use of a drug the particular state of relaxation which we were attempting to accomplish. We have observed for some years that most habitually tense or anxious individuals may quickly understand that they are to relax, but do not know what the sensations or experience of relaxation are. This drug gave us an opportunity of showing these people in a very distinct, clear manner the exact feeling or emotion which we wished them eventually to attain. No drug has ever adequately accomplished this for us in an even similar manner. In the

TABLE 1.—DATA ON USE OF TOLSEROL IN 11 CASES

No.	*Pt's Initial*	*Sex*	*Age*	*Diagnosis*	*Range of Dosage (grams)*	*Best Level (grams)*	*Time on Tolserol (weeks)*	*Effects*	*Unusual Symptoms*	*Degree of Improvement*	*Remarks*
1.	R.W.	F.	44	Anxiety Tension State (obsessive)	¼–1	1	1	"Tired" "Heavy" "Relaxed" "Left shoulder good"	Some nausea	++	Case of 20 yrs. standing. Has extra-systoles–no effect noted
2.	D.L.	F.	38	Tension Depression	¼–4	3	8	"Light" "Easy" "Comfortable"	None	++++	Once had questionable brucellosis
3.	H.B.	M.	35	Tension Depression	¼–3	1	2	"Quiet" "Relaxed" "Happy"	None	+++	Was quite "spastic" greatly relieved
4.	O.Y.	M.	34	Tension Depression	¼–6	4	3	"Tired" "Relaxed" Euphoria	Neck would not relax	+	Always troubled with stiff neck
5.	H.J.	M.	29	Anxiety Tension State	¼–3	2	2	"Good feeling"	None	++	
6.	M.A.	F.	38	Anxiety Tension State	¼–4	3	3	"Relaxed"	Too heavy	+	
7.	F.C.	F.	34	Anxiety Tension State	¼–3	1	8	"Very relaxed"	None	++++	Moody–irritable before. Unusually good response
8.	H.N.	F.	26	Anxiety Tension State	¼–4	2	10	"Relaxed"	None	+++	
9.	H.D.	F.	29	Tension Depression	¼–5	3	4	"Relaxed" Less spasm	None	+++	Ocular pain relieved
10.	M.B.	F.	42	Anxiety Tension State	¼–2	2	8	"Very relaxed"	None	+++	Had schizoid tendencies

0.25 Gm. tablets used

carefully selected group of people on whom we used the drug, almost without exception, this characteristic, almost classical state of "relaxation" was obtained. In those already completely relaxed, Tolserol had no effect in the dosages used by us to date. We have tried both tablets and elixir and see no difference in either, except that the tablets are better tolerated.

As stated, we used only physically well and healthy patients. In recent

TABLE 2.—FURTHER DATA ON USE OF TOLSEROL

No.	*Pt's. Initials*	*Sex*	*Age*	*Diagnosis*	*Average dose (gm.)*	*Time on drug (weeks)*	*Degree of Improvement*	*Remarks*
1.	V.M.	F.	33	A.T.S.	1	2	+	None
2.	S.R.	F.	21	A.T.S.	¾	3	0	Had schizoid tendencies
3.	K.V.	F.	26	A.T.S.	1	3	*	Usually had good results but had extreme nausea
4.	M.T.	F.	48	Menopausal depr.	¾	2	+ + +	Inclined to habituation
5.	S.P.	F.	21	A.T.S.	½	3	+ + + +	
6.	M.S.	F.	42	Tension-depression	¾	4	+ + +	Eyes especially were better
7.	H.G.	M.	49	Tension-depression	1½	2	Questionable	Was actually better but inclined to discount any aid
8.	K.R.	F.	23	A.T.S.	½	12	+ + + +	Even took it to aid distress from earthquake
9.	P.E.	F.	22	A.T.S.	½	2	+ + + +	No effect on an allergic condition
10.	R.D.	M.	28	Tension-depression	¾	2	+	Family history of depressions Some question of this being cyclic
11.	H.M.	F.	54	A.T.S.	1½	8	+	Some question of this lady also having a narcolepsy
12.	H.F.	F.	26	A.T.S.	1	2	+ +	None
13.	H.R.	F.	24	A.T.S.	½	1	+ + +	No effect noted on a tremor
14.	H.J.	M.	44	A.T.S.	1	3	+	Always had gastro-intestinal distress
15.	M.C.	F.	37	Tension-depression	¾	3	0	May have been early menopausal type
16.	T.W.	F.	35	A.T.S.	1½	2	+	Would not take it regularly
17.	H.N.	F.	25	A.T.S.	1¼	1	+ + +	Some schizoid tendencies
18.	D.B.	F.	31	A.T.S.	½	2	+ + + +	Much relief from acute tension
19.	E.M.	F.	47	Menop.-depression	1	4	+ +	A cyclic type of depression This her 5th episode
20.	D.F.	M.	22	A.T.S.	2	3	+ + + +	Complained of gastro-intestinal distress if taken when not eating
21.	M.M.	F.	59	A.T.S.	2	3	+ +	Tolerated any dose
22.	H.D.	M.	45	Menop.-depression	½	1	+ + +	Found sleep much easier
23.	G.N.	F.	28	A.T.S.	½	12	+ + + +	Used in any period of tension
24.	M.C.	F.	26	A.T.S.	½	1	0	Unpleasant gastro-intestinal distress
25.	D.H.	F.	27	A.T.S.	1¼	3	+ + +	Dislike "numb feelings"
26.	D.S.	F.	26	A.T.S.	2½	4	+ + + +	Relief to spasm of lower back

Pts. 1–13 on 0.25 gm. tablets
Pts. 13–26 on 0.25 gm. capsules

TABLE 3.—DATA ON GROUPS NOT INCLUDED IN TABLES 1 & 2

Diagnosis	*Number of Cases*	*Average Dosage (grams)*	*Number Improving*	*Number Unchanged*	*Remarks*
A.T.S. Anxiety Tension States purely situational — 7 habitual or chronic—43	50	0.75–1.25	47	3	All 3 complained of nausea etc.
A.T.S. Anxiety Tension States chiefly obsessive—compulsive type	17	1.5	10	5	5 unchanged or unaffected 2 had extreme nausea
Tension type depression	9	1.0	7	2	1 nausea reported 2 no change 1 disliked nausea
Tension depression (menopausal age)	5	1.0–1.5	3+	1	1 no change 1 objectively better but subjectively not
Others					
Pre-schizophrenic makeup —2	7	.75–1.5	2	2	The pre-schizophrenic type showed best results
Undiagnosed anxiety —3					
Anxiety but large physical factor —2					

0.25 gm. tablets used

weeks, however, we tried it on one individual with basically organic distress. The man, referred to us for treatment of "over-emotionalism", was 66 years old, formerly engaged in capable professional activity. He had had hypertension for years and in March, 1948 (18 months ago), had a right sided cerebral accident in the thalamic area. A typical left thalamic syndrome existed. The man, cooperative and still intact intellectually, had tried many kinds of treatment. Psychotherapy did not aid him. Since we had nothing else to try, we placed him on from 1 to 3 gm. of Tolserol daily. The dosage was so divided that 3 or 4 tablets were taken 2 or 3 times in 16 hours. The relief was immediate and very satisfactory from clinical observation and the patient's own story. He still takes it regularly. This case is mentioned only for its clinical interest.

Summary. We have used Tolserol on a large group of individuals suffering from various stages of what we commonly call in medicine "anxiety tension states". The individuals selected for investigation were all physically healthy, intellectually sound, men or women engaged in active living, working, or otherwise maintaining themselves substantially, who had been referred for psychotherapeutic treatment to clear up varying states generally described as anxiety tension reactions. Tolserol was given to those people selected because of their tremendous need for obtaining some particular state of relaxation, because we were seeing them daily and believed they could most honestly report back to us their typical reactions, and who would be most nearly free of any element of suggestion. Almost without exceptions our findings were that these people obtained with Tolserol a rather classical state of relaxation, characterized by feelings of warmth, numbness, euphoria, a feeling of letting down, all of the sensations commonly seen in individuals who are pleasantly and comfortably at ease. The compound was given to those people at

about the time they would otherwise be practicing letting down and was used almost entirely to help them find, in the majority of instances for the first time, what a state of relaxation really was. The average dose was .75 to 1.5 gm. daily for 10 days.

Conclusion. Tolserol offers to us for the first time an opportunity to demonstrate to the average individual suffering from any type or complication of an anxiety tension state, the type or amount of feeling of relaxation that we are attempting to teach that individual by a prolonged type of re-educative or psychotherapeutic program.

We wish to emphasize emphatically that in our experience Tolserol can best be used to demonstrate this state of relaxation or comfort. It is not, and we doubt if ever will be, properly used to relieve symptoms associated with an anxiety tension state, such as the average sedative does. Its place and its value is in its ability to demonstrate what can be accomplished eventually by re-educative or psychotherapeutic measures. To accomplish this illustrative point it is an extremely valuable and useful drug.

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A STUDY OF ATHEROSCLEROSIS IN A GROUP OF DIABETIC PATIENTS

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The rapidly rising incidence of arteriosclerosis and its complications as a leading cause of death has drawn the ever increasing interest of investigators. Since arteriosclerosis is protean in its manifestations, one should make every possible attempt to discover its presence. The aim of the present study is the recognition of arteriosclerosis so that "we may avert to the best of our ability the impending peril of clogged and rigid vessels"[35].

For this study of arteriosclerosis it seemed appropriate to select a group of patients in whom the incidence of the disease is known to be unusually high as, for example, in diabetes mellitus[11,15,22,29,30]. "Arteriosclerosis" is a general term which has been loosely applied to lesions of either the intima or media of arteries. Whether medial or intimal sclerosis prevails in a given artery seems to depend on the anatomic structure of the vessel. Elastic arteries such as the aorta and the adjacent great vessels are usually affected by intimal sclerosis, whereas in the muscular arteries of the extremities medial calcification, the so-called Mönckeberg's sclerosis, is the predominant lesion. These 2 processes are apparently unrelated, even though they may occur together frequently. It should be stressed that medial sclerosis is a benign process, whereas the intimal lesions of atherosclerosis produce the complications resulting in loss of life and limb. Since there is no question as to the presence of atherosclerosis in the full-blown vascular accident, the problem was to identify the process prior to the occurrence of such episodes. With this thought in mind, a group of 89 unselected patients attending the Diabetes Clinic of our hospital were studied. Their ages ranged from 18 to 91, the great majority exceeding 50 years of age.

Diagnostic Procedures and Results. Upon reviewing the generally accepted criteria for the diagnosis of arteriosclerosis we found that each had certain limitations and that some had to be reevaluated. In an examination of arteriosclerosis it is of prime importance to differentiate intimal and medial sclerosis. Palpation of the superficial arteries such as the radial and brachial is of little help in the detection of intimal changes because the lesion in these vessels is almost invariably medial sclerosis. On the other hand, deeply situated vessels in which atherosclerosis is present do not readily lend themselves to physical examination, and yet it is in these vessels in which the most important lesions occur.

Our approach to the present study was based on the following premises.

Although atherosclerosis is usually considered a generalized process, we were impressed with the fact as shown previously[14], that atheromatosis appears to be localized in two principal areas of the arterial tree: 1, The thoracic aorta, its adjacent great vessels and such important branches as the coronary artery, the carotid artery and its cerebral branches: *proximal (central) atherosclerosis*, and, 2, The abdominal aorta, the pathologic processes of which are intimately associated with atherosclerosis in the iliac and femoral arteries and their branches: *peripheral (distal) atherosclerosis*. The clinical procedures employed herein were also subdivided as to whether they applied to one or the other area. Each finding was carried out and corroborated by two or more of the examiners.

1. Proximal (Central) Atherosclerosis: Aorta and Great Vessels. The classical form of atheromatosis is found in the arch of the aorta and the adjacent great vessels which *per se* are rarely the site of vascular accidents. Still there is a fairly close correlation between the presence and severity of intimal changes in the aortic trunk and its branches such as the coronary arteries and the cerebral arteries. Although Warren[35] emphasizes the parallelism between the incidence of sclerosis in the aorta and the coronary arteries, the occurrence of atheroma in the coronaries alone is well known and requires no special comment. Provided such regional exceptions are taken into proper account, it may be assumed that demonstrable atherosclerosis in the upper aorta is a good index of the process in the tributaries.

Along with intimal sclerosis, degenerative changes are also found in the media of the aorta as early as the 35th year of life (Klotz[19]). *Pari passu* with advancing age, these medial changes are progressive and are the ones which bring about a gradual loss of elasticity of the vessel with increased tortuosity, elongation and dilatation.

Procedures Employed for the Detection of Proximal Atherosclerosis. *a, increased width of the aortic arch; b, calcification of the thoracic aorta; c, carotid-sinus-pressure test; d, supraclavicular pulsations; e, accentuation of the second aortic sound, f, the blood pressure; g, electrocardiogram.*

a. *Increased Width of the Aortic Arch Measured by Percussion and Roentgen-ray, 83 Cases* (93.1%). Insofar as the thoracic aorta is concerned, the only segment available to the examiner is the arch. Two procedures were used for the measurement of the aortic arch: percussion of the aortic dulness and measurement of the width of the arch on the chest film. According to Norris and Landis[19], in the normal individual the transverse area of dulness at the second costal cartilage measures 4.5 to 5.5 cm. by percussion. Any increase in the size of this area, especially to the right of the sternum is interpreted by them as being indicative of dilatation of the aorta. In our series extension of dulness to the right was a very infrequent finding. However, in the majority of cases there was a distinct increase of the percussion dulness to the left of the sternum just beneath the clavicle. In the chest film, an increase in the diameter of the arch is evidenced by the aortic knob and its point of greatest departure from the midline (dorsal spine) can usually be measured (see Ungerleider[34]).

Any increase in measurement to the left of the sternum over 2.5 cm., by either method or both, an arbitrary figure based on our experience, is interpreted here as dilatation of the aortic arch. A close correlation was noted between the percussion measurements and the measurements of the aortic arch on the Roentgen-

ray film. In 32% of the cases the measurements were identical. In 60% of the cases the difference noted was 0.5 cm. or less.

In our series, a definite aortic knob was present in 83 cases (93.1%, Table 1) and was absent in 5 patients all of whom were below the age of 40. This compares very closely with the figures on arteriosclerosis of the aorta in Warren's autopsy material, approximately 90%[35]. Despite the very high incidence of increased aortic dulness or enlargement by roentgenography, its value as an index of generalized atherosclerosis should not be overemphasized. The demonstration of a well defined aortic knob is to be interpreted as an attribute of senescence in the diabetic and the nondiabetic alike, and should be used only as an adjunct to other more significant signs.

b. *Calcification of the Thoracic Aorta by Roentgen-ray, 37 Cases* (41.5%). The finding of calcified plaques in the aortic knob in the chest film is a valuable sign of atherosclerosis, and certainly there is no better means of demonstrating atherosclerosis in its advanced stages. The rather high incidence of this finding is striking although sufficient emphasis has not been given to it in the current literature.

TABLE 1.—FREQUENCY OF DETECTION OF ARTERIOSCLEROSIS BY VARIOUS DIAGNOSTIC PROCEDURES

PROCEDURES	CASES	PERCENT
1. MEASURE OF AORTIC KNOB	83	93.1
2. POSITIVE CAROTID SINUS PRESSURE TESTS A. TYPE I – 27 CASES 30.3% B. TYPE II – 17 CASES 19.1% C. TYPE III – 17 CASES 19.1% D. NEGATIVE-26 CASES 29.2%	61	68.6
3. PALPABLE SUPRACLAVICULAR PULSES	51	57.4
4. CALCIFICATION OF ABDOMINAL AORTA	51	57.4
5. CALCIFICATION OF PELVIC VESSELS	50	56.6
6. CALCIFICATION OF FEMORAL ARTERIES	49	55.0
7. ACCENTUATION OF AORTIC SECOND SOUND	44	49.4
8. EVIDENCE OF PERIPHERAL VASCULAR DISEASE	41	46.0
9. FUNDOSCOPIC EVIDENCE OF ARTERIOSCLEROSIS	39	43.8
10. CALCIFICATION IN AORTIC KNOB	37	41.5
11. ABNORMAL ELECTROCARDIOGRAPHS	22	24.7
12. BLOOD PRESSURE		
A. ARTERIOSCLEROTIC	26	29.2
B. HYPERTENSIVE	29	32.6
C. NORMAL	34	38.2

c. *Carotid-Sinus-Pressure Test, Positive in 61 Cases* (68.6%). The *modus operandi* and significance of the carotid-sinus-pressure test in the detection of atherosclerosis of the thoracic aorta and the great vessels have been presented in detail previously[14,36]. An intimate relationship was shown to exist between advanced atherosclerosis of the upper aorta and its large branches and a positive carotid sinus reaction.

Three types of responses were observed: 1, A cardiac standstill or a very marked bradycardia which was attributed to an associated coronary sclerosis; 2, a prolonged drop in the systolic blood pressure of 20 mm. of mercury or more sustained for at least 3 minutes; and, 3, a combination of the bradycardic response with a prolonged fall in the blood pressure. As previously pointed out, the vasodepressor response in particular is indicative of proximal atherosclerosis.

In the course of the present study, it was found that the use of an oscillometer greatly facilitates the procedure. In performing the test, the cuff of the oscillometer applied to either arm is inflated to a point midway between the subject's systolic and diastolic pressure. Upon the application of pressure to the carotid sinus, a positive cardioinhibitory reaction is clearly shown on the oscillometric scale either by complete cessation of the oscillations of the needle (standstill) or by a decrease in the rate of the excursions (bradycardia). The oscillometer while in position can also be used to take the blood pressure readings to ascertain the vasodepressor effect (drop in blood pressure).

The high incidence of positive carotid-sinus tests (61 cases) in this series of diabetic patients was somewhat unexpected but, if anything, these figures are conservative in view of the difficulty in finding the carotid sinus in certain individuals. This was clearly brought out in 10 patients in whom the carotid-sinus-pressure test was originally negative, but on retesting gave 8 positive responses. From these results it appears that the carotid-sinus-pressure reaction is a valuable test for proximal atherosclerosis. We would stress the importance of doing this test carefully and repeating it several times on both sides, if need be, before concluding that it is negative.

d. *Supraclavicular Pulsations, 51 Cases* (57.4%). Norris and Landis[19] mention visible pulsations in the suprasternal notch and in the right supraclavicular fossa in association with aortic sclerosis. In our experience visible pulsations in these areas proved to be an infrequent occurrence as compared with positive palpatory findings. The subclavian artery pulse, ordinarily inaccessible in the normal individual, is frequently palpable in patients with advanced atherosclerosis[14]. The pulsation is expansile and can be felt midway between the sternum and the acromial process just above the clavicle. Once the examiner becomes familiar with this finding, it can be readily detected. One must be careful not to confuse the heaving sensation of this abnormal subclavian pulsation with other less forceful pulsations which may be observed in the neck of normal individuals and in persons with unstable vasomotor systems.

The explanation of the abnormal supraclavicular pulsation is fairly obvious. In atherosclerosis of the arch of the aorta, the vessel, being elongated and dilated, assumes a higher position in the thorax, so that the subclavian arteries are elevated and more readily palpated. Furthermore, these tributaries are also affected with atherosclerosis[17] which enhances their palpability. In the presence of palpable subclavian artery pulsations one may infer, therefore, that the thoracic aorta and the great vessels are sclerotic and displaced, provided anatomic anomalies, hypertension and syphilis are taken into consideration.

The presence of subclavian pulsations in two-thirds of our patients above 50 years of age is impressive. It is significant that in 14 patients below the age of 50, the subclavian pulsa-

tions were present in only one, and he had a strongly positive serologic test for syphilis. In our opinion the abnormal supraclavicular pulsations deserve high rank as a diagnostic criterion of proximal atherosclerosis.

e. *Accentuation of the Second Aortic Sound, 44 Cases* (49.4%). In patients with atherosclerosis of the aorta the second aortic sound may be sharply accentuated, high-pitched or have a tambour-like quality. This sign was detected in 44 of the 89 patients (49.4%) in our series. Despite the high incidence of the accentuated second aortic sound, its diagnostic value for atherosclerosis is somewhat limited, as this sign is also present in about two-thirds of the cases of hypertension[19]. However, in the absence of hypertension, syphilis, malposition of the aorta, and the like, the accentuated second aortic sound can be considered specific for atherosclerosis of the aorta.

It is of interest that the aortic second sound was audible in the suprasternal notch in 6 of 9 cases in which it was inaudible in the usual location.

f. *Blood Pressure—High Systolic, Low Diastolic Readings in 26 Cases* (29.2%). It is generally agreed that a high systolic, low diastolic pressure should not be classed as true hypertension, but rather should be correlated with underlying atherosclerosis of the aorta and its large branches (so called systolic hypertension). By contrast, true or essential hypertension with characteristic elevations in both the systolic and the diastolic levels is usually associated with arteriolar disease. In other words, the hypertension associated with atherosclerosis and that with arteriolar disease had best be regarded as two distinct entities. The manner in which atherosclerosis affects the dynamics of the blood pressure has been reviewed recently by Zeman and Schwartz[41]. With advancing age the aorta may become rigid and dilated and the effects of these factors on the blood pressure tend to produce a high systolic and a rather low diastolic reading.

An attempt has been made in our group of diabetic patients to separate the obviously normal, the hypertensive and the atherosclerotic blood pressure types. Patients with a systolic pressure above 150 and a diastolic pressure of 90 or less were classified as atherosclerotic, and those with a diastolic pressure above 90 were placed in the hypertensive category. We found 26 patients (29.2%) with the characteristic systolic hypertension, 29 patients (32.6%) with true hypertension and 34 (38.2%) normals. It is realized that the above criteria were applied arbitrarily and that many patients in the so-called hypertensive group with diastolic pressures just above 90 undoubtedly would have dropped either into the normal or the atherosclerotic classification under better basal conditions. Incidentally, Major's[24] findings of a higher systolic blood pressure in diabetic as compared with nondiabetic patients, in our opinion, may be explained by the greater incidence of atherosclerosis in diabetics generally.

Inasmuch as atherosclerosis seems to be associated with all ranges of blood pressure, the latter is not a reliable indicator of proximal atherosclerosis.

g. *Electrocardiogram.* As mentioned above, the incidence of coronary atherosclerosis parallels more or less that of atherosclerosis in the thoracic aorta and the adjacent great vessels. On this basis it might be permissible to infer from the presence of proximal atherosclerosis that the coronary arteries are similarly involved. Still, because of the occasional appearance of coronary atherosclerosis without any sclerosis in the aorta, and in view of the proven high mortality rate from coronary atherosclerosis in diabetes mellitus[4,12,26,31,35].

39, it was deemed advisable to attempt to make a more specific diagnosis. Therefore, electrocardiograms were taken on every patient and were interpreted as abnormal in 22 instances (24.7%). Of these, 16 patients had evidence of myocardial injury consistent with coronary sclerosis, 2 showed auricular fibrillation, 2 had bundle branch block, and 2 showed the findings of old myocardial infarctions. In these cases the electrocardiographic findings can be related to underlying coronary sclerosis. One patient with rheumatic heart disease (mitral stenosis and auricular fibrillation) with an abnormal electrocardiogram was excluded from this group. Cases with simple left axis deviation were not considered abnormal.

It is interesting to compare the electrocardiographic findings with the cardio-inhibitory reaction following carotid sinus pressure. In 61 cases with positive carotid sinus reactions 44 had a definite cardio-inhibitory response. As stated previously, a marked cardio-inhibitory reaction upon carotid sinus

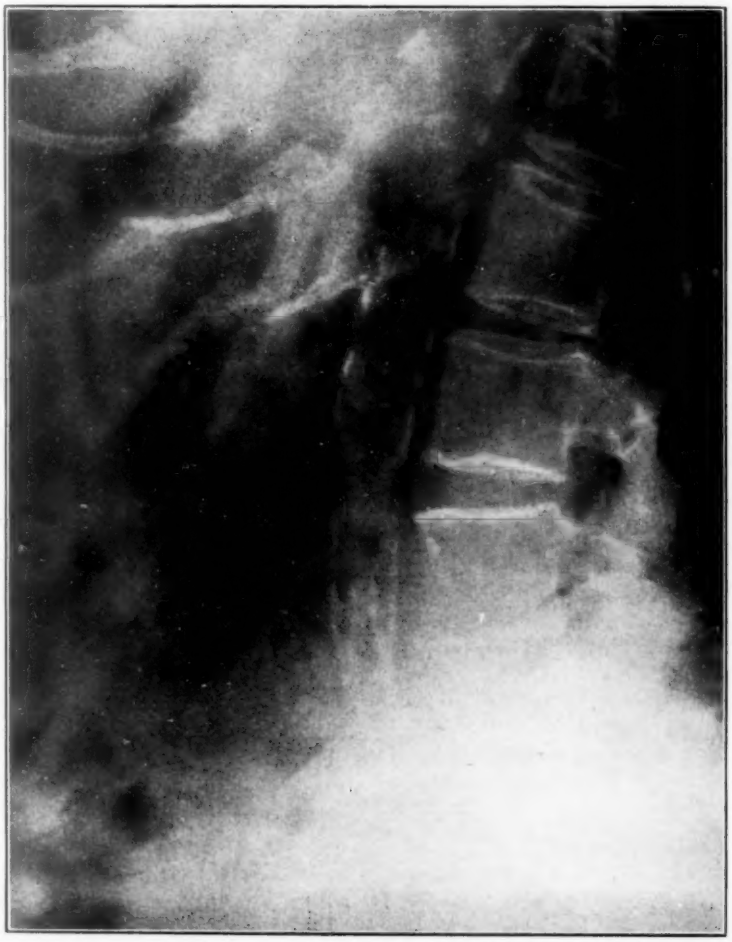

FIG. 1.—Lateral view of the lumbar spine showing marked atherosclerosis of the abdominal aorta.

pressure indicates ischemia of the myocardium and the conduction system and, by inference, coronary atherosclerosis[8,33]. It is of interest that 33 of the 44 patients with cardio-inhibitory responses had normal electrocardiograms; on the other hand, of the 22 patients with abnormal electrocardiographic records, 12 had marked cardio-inhibitory reactions. On the basis of the above hypothesis one may conclude that the carotid-sinus-pressure test is a sensitive indicator of myocardial damage and inferentially of coronary atherosclerosis.

2. Peripheral (Distal) Atherosclerosis: Abdominal Aorta, Iliac, Femoral Arteries and Their Branches. It is *a propos* to stress the fact that the most advanced atherosclerotic changes are usually found in the abdominal aorta (Ophüls[27]). In a previous paper, the view has been presented[14] that atherosclerosis in the lower extremities is part of descending process extending from the abdominal aorta into the iliac and femoral arteries. In fact, Keith and Horton[18] have reported cases of intermittent claudication in which the only objective finding is the presence of calcification in the abdominal aorta by Roentgen-ray.

Procedures Employed for the Detection of Peripheral Atherosclerosis. a, Roentgen-ray; b, Clinical examination.

a. *Roentgen-ray of the Abdominal Aorta, Pelvic and Femoral Arteries.* In the lateral views of the lumbar spine calcified intimal plaques are readily discernible in the abdominal aorta (Fig. 1). As emphasized above, the calcification which occurs in the aorta is intimal and was present in the roentgenograms in 51 of our cases (57.4%, Table 1).

The principal type of arteriosclerosis in the iliac and femoral arteries is Mönckeberg's (medial) sclerosis. In 345 persons Lundsgaard and Rud[23] found medial calcification by Roentgen-ray in the femoral and brachial arteries of 52% of the men and 9% of the women. Even more striking are the results of pathologic studies. Mönckeberg[25] found 55 cases of medial calcification in 130 cases which he examined. Of these, the femoral artery was involved in 51, the tibial in 36, and the radial in 21. In 3000 cases, from 30 to 80 years of age, Lange[20] reported the incidence of medial sclerosis to be as follows: 1, lower femoral artery 97%; 2, posterior tibial artery 87%; 3, anterior tibial artery 83%; 4, upper third of femoral artery 57%; 5, radial artery 18%; 6, Ulnar artery 14%; 7, popliteal artery 9%; 8, brachial artery 2%. From these data it is evident that medial calcification is a physiologic process especially in the arteries of the legs and begins early in life. It naturally follows that the type of calcification observed in the Roentgen films of the femoral and tibial arteries of any older group such as ours is much more likely to be medial than intimal.

According to Bowen and Koenig[6], an even higher frequency of calcification occurs in the leg arteries in diabetes mellitus than in non-diabetic individuals. In longstanding diabetes, the incidence of medial calcification was 93% in one series[2]. In our material calcification was present in the pelvic arteries in 50 cases (56.6%) and in the femoral arteries in 49 cases (55%).

In diabetes mellitus, however, and also in nondiabetic individuals with occlusive vascular disease, medial calcification in the iliac and femoral arteries is frequently associated with atheromatosis. Allen *et al.*[1] attempt to differentiate patchy areas, which they interpret in the Roentgen films of these arteries as atherosclerotic plaques, from the diffuse more or less continuous calcification of medial sclerosis (Figs. 2 and 3). We were unable to distinguish the 2 processes in our

Roentgen films of the pelvis and legs owing to overlying medial calcification. In order to identify the type of calcification seen in the Roentgen films of the leg, 5 amputated gangrenous limbs were carefully dissected. Almost invariably the calcification was medial and occurred in continuous sheets and in isolated patches. Consequently, in most of the patients, it was virtually impossible to differentiate atherosclerosis from medial sclerosis in the pelvic and femoral arteries by Roentgen-ray.

b. *Clinical Examination of the Arteries of the Lower Extremities*: *Circulatory Impairment in 41 Cases* (46%). Since the calcification seen in the roentgenograms of the lower extremities need not necessarily point to an occlusion of the arteries and, as shown above, may not even represent atherosclerotic plaques, it becomes all im-

FIG. 2.—Flat film of the pelvis showing sclerotic changes of the pelvic vessels.

portant to determine by clinical methods the degree of local circulatory impairment.

A routine examination was done on every case by one of us (LJM) who is interested in diseases of the peripheral vessels. The following is an outline of the examination performed:

1. History of intermittent claudication, rest pain.

2. Inspection of skin, nails and hair; presence of varicosities and ulcerations; palpation for temperature changes, arterial pulses.

3. Color changes on elevation and dependency; venous filling time.

4. Oscillometric examination of the arms, forearms, wrists, thighs, and the legs below the knees and above the ankles.

By these procedures, 41 cases (46%) of the group were found to have definite impairment in some portion of the arterial tree of the lower extremities.

FIG. 3.—Film of thigh showing predominantly medial sclerosis.

These figures correspond very closely with those of Pearl and Kandel[28] who found arteriosclerosis obliterans in 50% of 100 diabetic patients.

Of the 41 patients showing occlusive phenomena, Roentgen-ray films revealed calcification in the abdominal aorta in 27 cases (65.8%), in the pelvic vessels in 30 cases (73.1%), and in the femoral arteries in 31 cases (75.6%). As can be seen in Table 2, the incidence of calcification in these vessels is much greater in the patients with vascular impairment than in those in whom no impediment was found by clinical examination. In the femoral arteries the incidence of calcification in the obstructed group is actually twice that of the unobstructed group.

TABLE 2.—CIRCULATORY IMPAIRMENT OF THE LOWER EXTREMITIES AND ROENTGEN-RAY FINDINGS

	IMPAIRED CIRCULATION 41 CASES	NO IMPAIRED CIRCULATION 48 CASES
CALCIFICATION IN THE AORTA	27 CASES 65.8%	22 CASES 45.8%
CALCIFICATION IN PELVIC VESSELS	30 CASES 73.1%	22 CASES 45.8%
CALCIFICATION IN FEMORALS	31 CASES 75.6%	17 CASES 35.4%

An important corollary of occlusive arterial disease of the lower extremities is its relation to atherosclerosis elsewhere in the body. We agree with Friedman[13] that arterial occlusion of the lower extremities may be taken as "*prima facie* evidence" of severe atherosclerosis not only in the arteries of the legs but in the coronary and other important arteries as well.

3. *"Arteriosclerotic" Changes in the Fundi, 39 Cases* (43.8%). The fundi of every patient in this series were examined by a qualified ophthalmologist paying special attention to the question of retinal sclerosis. In 89 cases there were 39 instances where a diagnosis of arteriosclerosis of the retinal vessels was made. Further, it was found that retinal sclerosis was equally distributed in the group as a whole, that is, there was no relation to atherosclerosis in other parts of the body. Since the small retinal arteries and arterioles have very little structural relationship to the elastic and muscular arteries, it is not surprising that there is so little correlation between retinal sclerosis and atherosclerosis elsewhere. Although the ophthalmoscopic examination proved to be of little diagnostic value in determining the presence of atherosclerosis in our patients, this need not necessarily detract from its usefulness in the diagnosis of other pathologic states.

Discussion. The complexity of the problem of arteriosclerosis is illustrated by the divergence of opinions on the subject among various writers. For all practical purposes medial sclerosis may be set aside, inasmuch as in itself the process causes no interference with blood supply. Therefore, our efforts have been confined to the consideration of atherosclerosis.

In reviewing our results it was evi-

dent that not all the generally accepted methods for the diagnosis of atherosclerosis were of equal clinical value. It was found that the following procedures gave the most reliable information as to the presence of atherosclerosis: 1, the carotid-sinus-pressure test; 2, palpation of pulsations in the supraclavicular fossae; 3, visualization of plaques in the aortic arch by Roentgen-ray; 4, Roentgen-ray of the abdominal aorta; 5, clinical examination of the lower extremities.

The first 3 procedures when positive are indicative of proximal (central) atherosclerosis and, by inference, of atherosclerosis of the coronary arteries and other branches of the large elastic arteries. The remaining 2 procedures when positive are indicative of atherosclerosis of the abdominal aorta and its branches, especially the iliac and femoral arteries, and may be conveniently termed distal or peripheral atherosclerosis.

The practical application of these methods for the detection of atheromatosis is in general use at present in our Diabetic Clinic. In our opinion, if positive results are obtained by one or more of the above procedures, a diagnosis of atherosclerosis is warranted. In the present series, 79 subjects (88.7%) showed evidence of atherosclerosis by these methods of examination.

In the course of the study, the problem of occlusive vascular disease of the lower extremities took on some new aspects. On the basis of the prevailing literature[1,27] we had gained the impression that the occlusive processes in the leg arteries are the result of thrombi usually associated with atheromatous plaques. According to Boyd[7], in limbs amputated for senile or diabetic gangrene the lesions begin with "an atheromatous change which, in such a vessel as the anterior tibial, may cause such a degree of narrowing as to lead to gangrene, with or without thrombosis." As Ophüls put it[29], "the final complete closure is usually due to thrombosis."

These views are not confirmed by our pathologic findings. In 5 consecutive amputated gangrenous legs, 3 in diabetic and 2 in nondiabetic patients, there was no evidence of either atheroma or thrombi in the strict sense of the word. Instead, the peroneal, anterior and posterior tibial arteries were completely obliterated by a *solid fibrotic cord* traversing almost the entire length of the involved arteries. In the microscopic sections an enormously thickened intimal layer was present and the remaining lumen was completely filled with fibrous tissue (Figs. 4 and 5). It is of course possible that this was an old organized thrombus. We do not subscribe to this viewpoint which will be covered more fully in a future publication.

The literature makes only slight reference to this point, although in 1901 Bunge[9] and in 1926 Borchardt[5] described a similar fibrotic closure of arteries. In the recent literature Sappington and Fisher[32] have emphasized fibrotic occlusion as a cause of gangrene. Of especial significance is the low incidence of atheroma in their material of 44 gangrenous legs. Karsner[16] substantiates the fibrous character of the occlusive lesion in the leg arteries. He specifically states that this is "a purely productive process with growth of connective tissue and without atheroma or calcification." Although the number of cases to date is small, the pathologic findings of fibrosis are so consistent that a basic pattern appears to be present.

The finding of fibrosis in the arteries of the lower leg is in marked contrast to the changes in the arteries above the knee, in which the predominant lesion proves to be atherosclerosis with or without medial sclerosis. This fact is

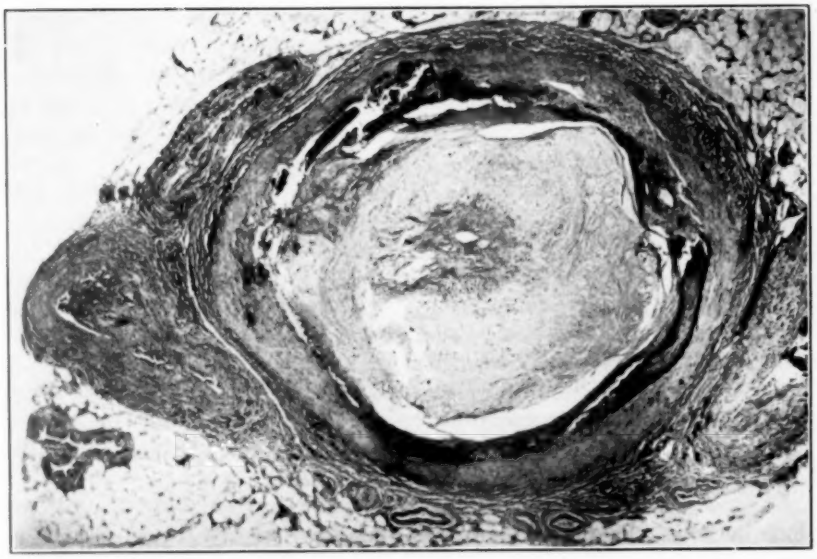

FIG. 4.—Posterior tibial artery—midportion. Cross section of the artery reveals very marked proliferation of the intima consisting of dense fibrous tissue which completely occludes the vessel lumen. Slight calcification is noted in a portion of the media; no changes in adventitia.

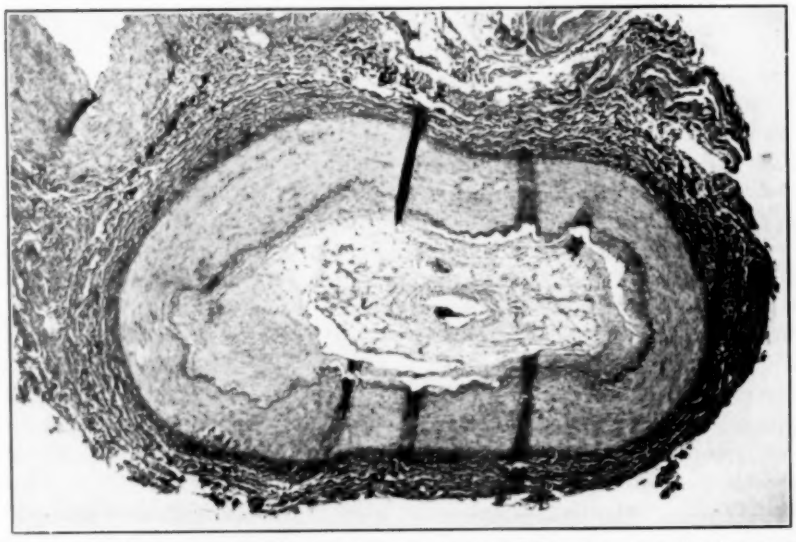

FIG. 5.—Anterior tibial artery: distal portion. Cross section of the artery reveals almost complete obliteration of the lumen by a dense proliferation of fibro-capillary tissue in the intima. No changes in the media or adventitia.

most emphatically illustrated in Sappington's group of amputated gangrenous limbs[32] in which an incidence of 70% for atheroma in the femoral and popliteal arteries is reported, though the lumina of the vessels remained patent. In view of the concurrence of atheromatosis in the thigh and fibrosis in the same leg, the question arises as to a possible relationship between the 2 processes. The fact that one type of lesion prevails in the arteries of the thigh (atheroma) and an entirely different process in the arteries of the legs (fibrosis) may solve the confusion in the nomenclature of the obliterative diseases. Virchow in his day interpreted the occlusive lesions in the vessels as being partially inflammatory (endarteritis obliterans). Only recently Virchow's terminology was changed to arteriosclerosis obliterans[1]. We would propose the term "arteriofibrosis obliterans" as being more applicable to the type of lesion present.

Further to illustrate the difficulties encountered in analyzing the many problems of arteriosclerosis, one need only refer to the vascular changes described in juvenile diabetics. For instance, in the experience of Priscilla White[37,38], retinal sclerosis is the most frequent sign of arteriosclerosis in juvenile diabetics (85%). According to this author, "Its importance as an index of total vascular disease cannot be over emphasized." The incidence of retinal sclerosis in her juveniles is about twice as high as in our series of predominantly aged diabetics. In this regard it is pertinent to note that pathologists themselves are unable to define retinal sclerosis to their satisfaction, and they suggest that unless the ophthalmologists can be more specific in their descriptions of arteriosclerosis in the retinal vessels, one cannot draw valid deductions from fundoscopic observations[3,21,40]. The lesions in the retinae of diabetics are those of the small blood vessels, namely, arterioles, capillaries and venules[29,38]. When capillary lesions, renal "intercapillary" lesions included, are classified as arteriolar sclerosis, it is only for the sake of convenience and not by reason of pathologic similarity. Therefore, it is stretching a point to include capillary, and even arteriolar lesions, under the heading "arteriosclerosis." Even experimentally produced arteriosclerosis does not affect arterioles and capillaries but only the larger arteries.

According to White[38], 70% of her cases showed calcification first in the vessels of the lower leg and subsequently in the iliac arteries and the abdominal aorta. It is especially significant that *no* cases of gangrene are reported in her series, which in itself speaks strongly against this calcification being atherosclerosis. In our adult group, as has been emphasized, medial calcification though prominent in the Roentgen films of the leg arteries in many patients is of secondary importance compared with intimal sclerosis and its complications such as gangrene. Incidentally, the existence of calcified plaques in the arch of the aorta, seen commonly in the older diabetics, was not demonstrable roentgenographically in any of White's cases.

The difference between the type of arteriosclerosis depicted in White's patients and the type which prevails in our cases points up the fact that there may be something distinctive about arteriosclerosis in young diabetics. From White's data it seems that the processes prevalent in young diabetic patients are essentially: *a*, a *capillary disease* (retinopathy, intercapillary glomerulosclerosis) and, in the case of the leg vessels; *b*, an earlier onset of and a more severe form of *medial calcification* than is usually found in normal persons. Hence, juvenile diabetics are

not simply a group of individuals in whom atherosclerosis so common in older persons has been accelerated. It is gratifying to find that Collens[19] has the same viewpoint on the subject. In his remarks on Dr. White's paper, he discusses the possibility that the renal and retinal changes in the young are "an entirely different disease from the arteriosclerosis which occurs in later life." He envisions the renal and retinal changes described by White as belonging to a syndrome which originates with the renal pathology of Kimmelstiel–Wilson's syndrome terminating in renal failure. As just pointed out lesions of the small vessels have an entirely different pathogenesis, localization and clinical significance and seem to be much more common in juvenile diabetics.

Unquestionably, the most important type of arteriosclerosis in diabetic patients is atherosclerosis, and such disabilities as coronary artery disease, cerebrovascular accidents and gangrene of the lower extremities result for the most part from changes of the intima. In our group of diabetics it is clear that atherosclerosis, as in any group of older individuals, is the prevailing lesion. It is atherosclerosis, then, which we have principally considered in the present study in contrast to recent publications[29,37,38] in which lesions of the small vessels are highlighted.

We are cognizant of the numerous studies on blood cholesterol and its relation to atherosclerosis. However, the subject does not fall within the scope of this paper, which stresses the physical signs of atherosclerosis.

It is realized that the clinical procedures for the diagnosis of atherosclerosis emphasized in this study have been made in a predominantly older age group. Still we think that this is a valid starting point for a means to the earlier detection of intimal changes in diabetics and nondiabetics alike.

Summary. 1. An attempt has been made to ascertain the presence of atherosclerosis in 89 unselected diabetic patients from the out-patient department. Five diagnostic procedures were found to be of special value:

(a) The carotid sinus pressure test (positive in 68.6% of the cases).

(b) Palpation of supraclavicular pulsations (present in 57.4% of the cases).

(c) Presence of calcification of the abdominal aorta by roentgenological studies (57.4% of the cases).

(d) Determination of occlusive arterial changes in the legs (present in 46% of the cases).

(e) Presence of calcification in the aortic arch in the chest film (41.5% of the cases).

2. From the functional viewpoint, of the two main types of arteriosclerosis, medial sclerosis is part of the ageing process and has no special clinical significance.

3. Arteriosclerosis of the intima occurs in two major areas: *a*, In the thoracic arch and its adjacent vessels, *proximal atherosclerosis*, and, *b*, in the lower abdominal aorta and its main branches, *distal atherosclerosis*.

4. The carotid sinus pressure test, supraclavicular pulsations and the presence of plaques in the aortic arch by roentgenography are valuable signs of proximal atherosclerosis.

5. Calcification of the abdominal aorta and clinical evidence of occlusive vascular disease in the lower extremities are of comparable value in the diagnosis of peripheral atherosclerosis.

6. The clinical examination of the lower extremities provides more information as to the existence of occlusive phenomena in the leg arteries than any other procedure.

7. In the dissection of 5 consecutive amputated limbs, it was found that the

cause of occlusion of the arteries is a characteristic fibrotic proliferation of the intima. The term "arteriofibrosis obliterans" is recommended for this process.

8. Of less importance for the diagnosis of atherosclerosis were the electrocardiogram, fundoscopic examination, Roentgen studies of the pelvic and leg arteries, accentuation of the second aortic sound and the blood pressure reading.

We are deeply indebted to Dr. B. S. Kline of the Department of Pathology, Drs. Mahrer, Krause and Lubert of the Department of Roentgenography and to the Cardiac and Ophthalmology Departments for their valuable assistance in the interpretation of our material.

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PATTERNS OF PLASMA PROTEIN CHANGES IN ACUTE POLIOMYELITIS PATIENTS: TREATMENT WITH BLOOD PLASMA*

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During the Los Angeles epidemic of 1948, 3165 cases of acute poliomyelitis occurred. Of these, 3094 were admitted, diagnosed, and treated in the Los Angeles County General Hospital. Such an unprecedented wealth of clinical material, seen in one hospital by one group of clinicians in a relatively short period, stimulated us to investigate certain basic physiologic and pathologic mechanisms not previously done. There were 612 bulbar poliomyelitis cases seen, of which 603 were treated in the Communicable Disease Unit. It was in this group that the morbidity and mortality were sudden and dramatic. Numerous questions arose regarding electrolytic balance in these cases, and it was soon learned there was no answer supplied by the medical literature as reviewed forward from 1877. Therefore, a study was planned to determine the status of the blood electrolytic patterns from the time of admission of the patient to the hospital until such time as he was discharged to other places. Because data pointing to aberrations in serum-protein patterns were accumulated rapidly, this problem was immediately investigated. It is with serum protein patterns in acute poliomyelitis patients that this report is concerned. Though the electrolyte studies are closely bound to this work, they will be published later. This report is offered now because of its therapeutic implications.

The study of each acutely ill patient was grouped into (a) blood-serum chemistry and (b) urine chemistry, and the procedures required were set up in chart-form to show continuous graphic data for each patient. The laboratory made the following determinations: blood serum chlorides, plasma bicarbonates, CO_2 combining power, serum sodium, serum potassium, whole blood potassium, serum proteins and

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partitions, whole blood pH, whole blood hematocrits, circulating ketone bodies, urine pH, urine bicarbonates, urine sodium, urine potassium, urinary chlorides, and urinary creatine and creatinine. These data will be covered in another paper. As data accumulated, it was noted at once that there were consistent aberrations in the serum albumin content of the blood, serum albumin values being lowered often to the point of albumin/globulin ratio reversal, findings consistent with those found in other illnesses in which peripheral edema plays a prominent role. It was further noted that these changes appeared unusually early in poliomyelitis, and they appeared to drop in values parallel to the increasing clinical severity of the illness. One of the authors (Eaton) further suggested that, on the basis of similar experience in other illnesses in which lowered serum albumin was correlated with altered osmotic equilibrium of body fluids and edema, this might account for some of the focal edema of poliomyelitis, attributed solely to the action of the virus in the past. He then theoretically postulated that these low serum albumin values were implicated in producing additional edema, and that it might be possible to stabilize and correct falling albumin levels by the administration of whole blood, blood plasma, or human serum albumin. Previously observed and reported instances of the value of plasma in the treatment of acute poliomyelitis (A.G.B.)[1] support this view. The objectives of this study were to determine: 1, What the serum protein patterns in acute poliomyelitis are; 2, Whether alterations from the normal patterns, when they occur, have any clinical correlation; 3, Can the observed patterns be altered by the administration of plasma or plasma substitutes; 4, Is the attempted serum protein level correction of any clinical value in the treatment of poliomyelitis?

Procedure. Certain difficulties limited the scope of the study early in its course. Clinical material was abundant, but it was impossible to obtain sufficient irradiated serum plasma to enlarge the series as desired. In fact, available supplies forced a limitation, both in terms of time and the amount of treatment. Any possible theoretical benefit from antibody content of utilized blood plasma was discounted and not regarded as pertinent.

This study is based on 75 clinical cases (28 treated, and 47 controls). All cases were admitted to the hospital during the 1948 epidemic, and each met the affirmatively accepted criteria for diagnosis; namely, typical history, classical physical and spinal fluid findings. No equivocal cases were used. All cases were confirmed, and isolated as having acute poliomyelitis, by the agents of the health departments concerned.

All these cases of poliomyelitis passed through the communicable disease admitting ward where they were completely examined and appropriate laboratory work, muscle checks and spinal fluid studies were performed by physicians working there, before they were admitted to the hospital. All cases included in this study were seen within 12 hours of admission by one of the authors (J. E. A.) and followed daily thereafter by him. Within 12 hours, each patient was seen by one of two trained physical therapists who completed the patient's "Muscle Grading" chart. Following the above procedure, all cases were arbitrarily placed in one of the 3 following categories for the purpose of this study:

1. MILD. Non-paralytic, pre-paralytic cases without bulbar involvement, or those with less than one-third of the total body musculature involved.

2. MODERATE. More than one-third of the total body musculature involved, or bulbar involvement present, but the patient not sufficiently ill to be placed in a respirator.

3. SEVERE. Paresis or paralysis of more than one-third of the body musculature; bulbar involvement necessitating use of a respirator, and usually tracheotomy.

Since the supply of blood plasma was limited, treated cases and controls were no longer alternated, but plasma therapy was reserved for severe cases. Cases accepted for inclusion in this series had blood samples taken immediately for protein determinations. The plan of procedure was as follows: 1. Daily serum-protein levels were made for 5

days. 2. On alternate days, specimens were taken until an additional 5 were secured. 3. If the patient remained available beyond the 14 day quarantine, specimens were taken every 3d day. 4. If the patient received blood plasma, a protein determination was done immediately prior to plasma administration. 5. TREATMENT. Each patient treated received daily injections of pooled human irradiated blood plasma in amounts calculated roughly at 5 cc. per pound of body weight for 5 consecutive days. However, no patient received more than 1000 cc. of plasma on any single day, with a few exceptions. 6. Each patient was rechecked by the same physical therapist on the 1st, 3d, 7th and 14th hospital day, and when possible, weekly thereafter.

All laboratory determinations were made in the research laboratory (A. L. C.), using the Howe[8] technique for the separation of albumin and globulin, and measured by the biuret method of Kingsley[9,10]. Blood samples showing hemolysis were discarded and fresh ones taken.

DATA. Of the 28 treated cases, 15 were grouped as severe, 9 as moderate, and 4 as mild. In the 47 control cases, 9 were severe, 13 moderate, and 25 mild. The serum albumin values used as "normal" were derived from a number of determinations by the same technique. The serum-globulin values are also available and will be discussed.

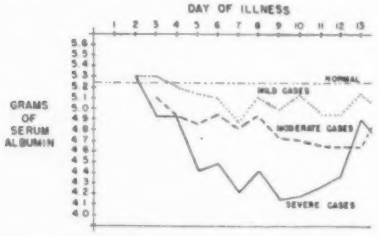

FIG. 1.—Serum albumin levels in poliomyelitis. Controls: 25 mild cases, 13 moderate cases, 9 severe cases.

Control Series. Fig. 1 presents graphic curves of average serum albumin levels in the untreated control series, classified according to severity. The protocols reveal that the serum albumin levels drop progressively each day, starting about the 3d day of illness (counting the first day of illness as that day on which the symptoms warranted diagnosis). The drop in albumin level is roughly proportional to the severity of the illness. By the 7th to 10th day of illness, the albumin level reaches its lowest value and tends to level off or swing upward (Table 1). Severe cases frequently not only show a drop in serum albumin of 1 or more gm. per 100 cc., but also an upswing of the globulin, which results at times in reversal of the A/G ratio.

Treatment Series. Figs. 2, 3, and 4 illustrate composite results obtained by using daily infusions of irradiated pooled human blood plasma at 5 cc. per pound of body weight. From the point of view of stabilizing or correcting depleted albumin levels, several facts become apparent, *e.g.*, in the mild cases it was possible to elevate the serum albumin levels above normal. Whether this is desirable or not remains to be proven; at any rate, mild cases probably can be given smaller amounts or the interval between infusions lengthened. In moderate cases, it was possible to elevate the diminished serum albumin level toward normal quite materially. For these moderate cases, the dosage used appears ade-

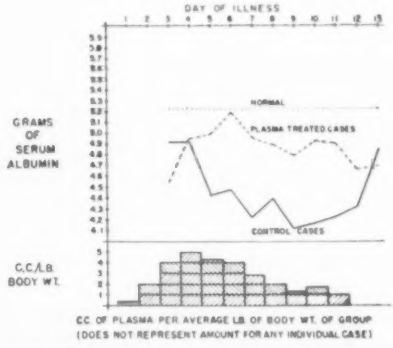
DAY OF ILLNESS
GRAMS OF SERUM ALBUMIN
NORMAL
PLASMA TREATED CASES
CONTROL CASES
C.C.A.B. BODY WT.
CC OF PLASMA PER AVERAGE LB OF BODY WT. OF GROUP
(DOES NOT REPRESENT AMOUNT FOR ANY INDIVIDUAL CASE)

FIG. 2.—Serum albumin levels in severe poliomyelitis. 9 control cases, 15 plasma treated cases.

TABLE 1.—ALBUMIN AND GLOBULIN VALUES IN 2 TYPICAL CONTROL CASES

CASE	DAY OF ILLNESS	SERUM ALBUMIN GRAMS/100 C.C.	SERUM GLOBULIN GRAMS/100 C.C.
QN 29 YR. MALE BULBO-SPINAL MODERATE	4	4.84	2.37
	5	5.02	2.42
	6	4.48	2.32
	7	4.38	2.22
	8	3.94	2.32
	11	3.84	3.27
	12	3.80	2.66
	13	3.73	2.90
T.K. 17 YR. FEMALE ASCENDING-SPINAL SEVERE	5	4.24	3.24
	6	3.98	3.10
	7	4.13	3.07
	8	4.06	2.63
	9	3.18	3.24
	10	3.57	3.32
	11	4.13	2.44
	12	4.15	2.53
	13	4.08	2.48

NORMAL: SERUM ALBUMIN - 5.26
SERUM GLOBULIN - 2.31

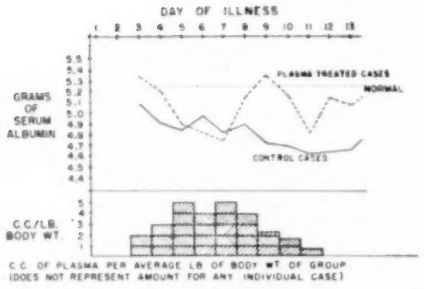
DAY OF ILLNESS
GRAMS OF SERUM ALBUMIN
PLASMA TREATED CASES
NORMAL
CONTROL CASES
C.C./LB. BODY WT.
C.C. OF PLASMA PER AVERAGE LB. OF BODY WT. OF GROUP
(DOES NOT REPRESENT AMOUNT FOR ANY INDIVIDUAL CASE)

FIG. 3.—Serum albumin levels in moderate poliomyelitis. 13 control cases, 9 plasma treated cases.

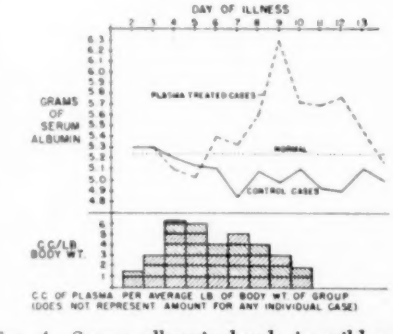
DAY OF ILLNESS
GRAMS OF SERUM ALBUMIN
PLASMA TREATED CASES
NORMAL
CONTROL CASES
C.C./LB. BODY WT.
C.C. OF PLASMA PER AVERAGE LB. OF BODY WT. OF GROUP
(DOES NOT REPRESENT AMOUNT FOR ANY INDIVIDUAL CASE)

FIG. 4.—Serum albumin levels in mild poliomyelitis. 25 control cases, 4 plasma treated cases.

quate. In the severe cases, 5 cc. per pound of body weight was inadequate though helpful. In spite of such doses, levels remained below normal, and when the supportive therapy was stopped, the serum albumin levels declined further. We think that serum albumin levels can be bolstered in these severe cases, but the doses did not exploit these possibilities to the fullest. Had maximal therapy been continued or even augmented, we believe more nearly normal serum albumin values would have been attained.

In either control or treated series, the globulin values of moderate and severe cases early begin to rise (See Fig. 5). Because of this rise in the serum globulins, total protein determinations are of little practical value in evaluating clinical progress; osmotic equilibrium is controlled very largely by the smaller albumin molecule. Actually, by the method used in this study, that fraction of the globulin known as the alpha globulin is salted out with the albumin; thus, the low values cited for albumin are in reality

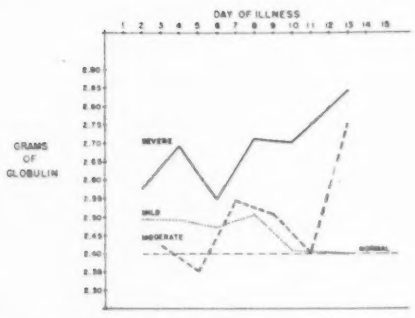

FIG. 5.—Serum globulin levels in control cases. 25 mild, 13 moderate, 9 severe.

even lower. It has been shown in studies of serum proteins by electrophoretic methods[4], that when serum albumin levels drop from any cause, the alpha globulins increase in amount. It was not thought technically feasible to correct our values in this respect.

Discussion. In regard to the fourfold objectives listed earlier, it can be stated on the basis of the data presented that: 1. The greater the clinical severity and involvement of the case, the more consistently will the serum albumin levels drop below normal. This drop occurs early, between the 1st and 3d day, and progresses unfavorably until the 10th day at least. These patterns, observed in 75 cases, appear so consistently that they are to be accepted as clinical facts until such time as additional studies in the future further confirm them or prove otherwise.

2. The deviation of the serum protein values from normal bears a linear relationship to clinical severity. *i.e.*, the more severe the clinical involvement, the less the amount of serum albumin present. The pattern of downward progression has been given. On a statistical basis, the consistency with which these findings will occur in a large series requires further study.

3. It is possible by giving blood plasma to retard the usual drop in the serum albumin level, and to raise lowered levels, in some instances to normal.

4. We think that giving blood plasma to moderate and to severe clinical cases of acute poliomyelitis is definitely valuable. We recognize the great difficulty in evaluating any single case, in predicting the progress of a given case with or without therapy, in presenting objective measurements of improvement or progression, and the danger of formulating opinions upon insufficient data or too few cases.

In keeping with scientific tradition, we attempted to obtain unbiased opinions of physical therapists in following muscle involvement and thereby approach a critical evaluation. These therapists were uninformed of the nature of the clinical studies undertaken. All severe cases were receiving parenteral fluids of one sort or another daily, so another bottle of a different sort created no particular impression. There remain, also, the opinions and the impressions of the senior authors whose experience with poliomyelitis encompasses not only these 3094 cases, but also epidemics occurring periodically for over 3 decades, as well as endemic cases seen in non-epidemic years. Evaluation of any new therapy which cannot be objectively measured is fraught with danger due to over-enthusiasm, and of this danger we are well aware. However, from clinical observations paralleling its use and the subsequent data obtained, we believe that the administration of blood plasma in large amounts, over suitable periods of time will prove life-saving in acute poliomyelitis.

CASE 1. M. W. Wh., f. Age, 18 years. Onset with backache for 5 days, headache, and generalized weakness for 2 days.

Physical Exam. Stiff neck and back; temp. 101.0° F.; hamstring tightness, weakness of triceps and quadriceps; superficial reflexes absent; deep reflexes absent in triceps, patellars, and achilles on left.

Spinal Puncture. Cells, 285/cu. mm.; predominently lymphocytes. Pandy test positive.

Diagnosis. Acute poliomyelitis, ascending, spinal type. Severe.

Course (see Fig. 6). The disease was arrested following initial administration of 750 cc. of plasma with gradual steady clearing of paralysis. Patient treated daily for 7 days. Removed from the respirator on the 32nd hospital day.

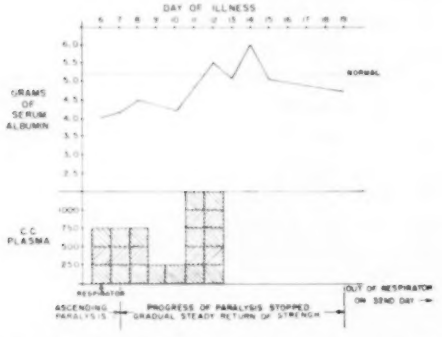

FIG. 6.—Case of M.W., 18 years, female, severe. Ascending spinal type.

IMPRESSION. Improved by plasma therapy.

CASE 2. B. S. Wh., f. Age, 13 years. Headache, fever, nausea for 4 days; stiff neck for 4 days; respiratory distress and dysphagia for 1 day.

Physical Exam. Temp. 102.0° F. Stiff neck and back; hamstring tightness; reflexes normal; paralysis of soft palate and right arm; diaphragmatic and intercostal paresis.

Spinal Puncture. Cells, 210/cu. mm. with 80% lymphocytes. Pandy test positive.

Course (see Fig. 7). Patient became comatose on the 3d hospital day and was thought to be in terminal stage. Generalized edema developed. Patient given 1000 cc. plasma when serum albumin level was 3.00 gm. per 100 cc. Patient regained consciousness in 24 hours with dramatic improvement which progressed favorably. At the conclusion of therapy, the patient seemed to maintain herself until suddenly, 10 days after the initial coma, she became suddenly cyanotic, went into circulatory collapse and died.

IMPRESSION. Initial benefit from plasma therapy with relapse after it was stopped. This case illustrates the previous statement that a consistent laboratory follow-up is necessary in every case. As the graphs illustrate, many of the severe cases are not capable of maintaining the temporary advantage provided by plasma therapy and will relapse unless more is given. In all probability, the

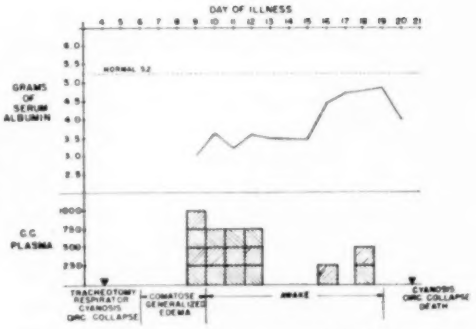

FIG. 7.—Case of B.S., 13 years, female, severe. Bulbo-spinal.

dosage of plasma was neither large enough nor given long enough to obtain maximal sustained benefit.

That serum protein levels drop in various acute infections and immediately after surgical operations is well known. This phenomenon has been referred to as "the reaction of injury", or the "catabolic phase of injury"[6]. In poliomyelitis, it is thought that the drop in serum protein levels occurs too soon in the course of the disease to ascribe it to malnutrition, though it is a fact that in the early febrile stage of severe poliomyelitis no food is given by mouth.

It is well known that edema occurs in such diseases as nephrosis, chronic liver disease, malnutrition of long standing, and that in these conditions when edema exists, there is depletion of serum albumin. The data in this report give evidence that poliomyelitis also causes profound hypo-albuminemia in its early acute phase. That edema plays any significant part in the production of paralysis in poliomyelitis is a concept that has ebbed and flowed, never having been either conclusively accepted or disproved. In 1907 Wickman[12] stated that edema of the central nervous system played a dominant role in producing paralysis. In 1949, Bodian[2] seems reluctant to accept this conclusion, although he does state that

" . . . It seems doubtful that nerve cell injury or destruction alone is responsible . . . since in many areas of severe nerve cell destruction, the inflammatory response is relatively quite mild." It is logical to accept that by the time a pathological section is prepared, the very processes used in tissue fixation might defeat an accurate estimate of edema. In view of the above it seems strange that till now, no data such as we present concerning serum albumin levels and their relationship to edema formation have previously been published concerning acute human poliomyelitis. This is all the more strange, as animal studies[5] have demonstrated that an acute drop in total serum albumin of 0.5 gm. per 100 cc., experimentally produced, will cause demonstrable pulmonary edema. The severe cases in this series repeatedly demonstrated rapidly developing drops in serum albumin levels of 1 or more gm. per 100 cc. blood serum.

Poliomyelitis is unique in that not only is the amount of paralysis present in the acute phase usually much greater than that during recovery, but also in that a very rapid improvement occurs frequently in the extent or amount of paralysis that has never been adequately explained. If the tremendous influence of osmotic equilibrium in the human body is considered, it becomes apparent that either a sudden drop or an elevation of the serum albumin level, with its proportionately great change in osmotic pressure, can give rise to sudden and dramatic changes in the condition of a patient, especially when these changes are interpreted with regard to edema formation within the central nervous system. The residual paralysis in any single patient represents the number of functional neurons destroyed in a certain location or locations of the central nervous system, minus a certain amount of physiologic adaptation and muscle re-education.

The presence of edema in the central nervous system affected by poliomyelitis has been adequately described by Courville[3] and many others both before and since. It is accepted by most that a certain amount of focal edema is initiated by the action of the causative virus and the attendant inflammatory response. Excessive edema fluid interposed between the neuron and its nearest capillary interferes with the oxygen-carbondioxide exchange. Nervous tissue, of all body tissues, is the most quickly damaged by anoxia and in the shortest time, particularly since additional anoxia may be present as a result of inadequate respiratory oxygenation or other factors. For this reason, it becomes vital to bring about resolution of central nervous system edema as quickly as possible. Should our hypothesis be further substantiated by subsequent studies, that lowered serum albumin levels are instrumental in producing additional edema, the value of serum albumin replacement in adequate amounts in the shortest possible time will have become fully established.

In a given case at a particular time, the degree of paralysis due to direct action of the virus and that due to edema cannot be determined by present methods. From the data in this report, the prevention of serum protein changes should aid in breaking the vicious cycle of edema and anoxia, and tend to reduce paralysis to that caused by the action of the virus on specific neurons. We believe this hypothesis to be feasible; that prompt action along these lines has made the difference in some cases between life and death; and that it may have materially affected the final degree of paralysis in the convalescent patient.

In the final evaluation of our data,

the plasma-treated cases were compared with the control cases in regard to their clinical course, as evaluated by the physical therapist previously mentioned. Beginning with the 3d hospital day, selected as such because plasma therapy was started on or before that time in nearly all cases, the observation of increased, unchanged, or decreased paralysis was made in each of the 3 arbitrary classifications of mild, moderate or severe (Table 2). Invariably the plasma-treated group revealed unquestionably superior results. This is particularly impressive in the severe group. Ninety per cent of the controls progressed as compared to 53% in the treated group. It is to be reiterated, however, that we are hesitant to stress these results because of our awareness that the series is small, and that there are no criteria for objective improvement which are indisputable.

TABLE 2.—CLINICAL RESULTS IN PLASMA TREATED AND CONTROL CASES

CLASSIFICATION	GROUP	NO. OF CASES	WORSE	UNCHANGED	IMPROVED
MILD	CONTROL	25	24%	68%	8%
	PLASMA	4	25%	50%	25%
MODERATE	CONTROL	13	30%	61%	9%
	PLASMA	9	33%	44%	23%
SEVERE	CONTROL	9	90%	0%	10%
	PLASMA	15	53%	20%	27%

WORSE REPRESENTS INCREASED AMOUNT OF INVOLVEMENT OR PARALYSIS
IMPROVED REPRESENTS DECREASED AMOUNT OF INVOLVEMENT OR PARALYSIS
THIS TABLE REPRESENTS CHANGES BETWEEN 3RD & 14TH HOSPITAL DAYS ONLY
BECAUSE PLASMA PATIENTS BEGAN RECEIVING IT ON OR BEFORE THE 3RD HOSP DAY

To workers in this field who may care to investigate this preliminary report further, we suggest some pertinent problems that go beyond our investigation, to wit:

1. It is not known how long the abnormalities in serum protein patterns remain in any single patient. At the conclusion of this study, most severe cases still demonstrated serum albumin levels below normal. Reports have been received from hospitals receiving these patients for long term chronic care, that some of these severely involved cases, judged to be stabilized, turned suddenly worse and died for no demonstrable reason.

2. It is not known what the result of treatment would be if each patient in the severe group were treated for longer periods, and possibly with larger amounts of plasma.

It must be borne in mind that we were aware of the sodium content of the plasma and were extremely reluctant to force large quantities of sodium.

3. It is not known if there is any appreciable effect from the antibody content of large amounts of blood plasma. We were unable to acquire sufficient human serum albumin, salt-free, to complete a series which would determine this factor.

We believe that cases which fall into our "mild" class probably will do well without plasma. On the other hand,

the arbitrary dosage of 5 cc. per pound of body weight seemed quite adequate for the "moderate" group. In the "severe" group, it is thought that 5 cc. per pound is insufficient and that 5 days of treatment are unquestionably too few.

This report deals only with one phase of the entire problem of metabolic changes in acute poliomyelitis patients and by no means brings out the magnitude of other changes such as those of the acid-base balance which are of utmost physiologic significance. Since, however, it deals with a problem not previously covered in the literature, and since it was easily amenable to clinical application without necessitating an elaborate research laboratory, it is felt that its presentation is warranted.

Summary. 1. A study of the serum protein patterns in 75 acute poliomyelitis patients was conducted. Daily protein determinations were carried out on 47 cases as controls, and 28 patients who received therapeutically large daily doses of pooled irradiated human blood plasma.

2. In general, the serum albumin fraction of the blood proteins dropped in a manner roughly parallel to the clinical severity of the case, beginning between the 1st and 3d days of illness and this drop reached a maximum between the 7th and 10th days.

3. The progressive drop in serum albumin levels was retarded, or prevented in some cases, by the administration of pooled irradiated blood plasma in amounts of 5 cc. per pound of body weight within 24 hours after it was given. This augmentation of serum albumin values is a temporary phenomenon requiring continuous support for an as yet undetermined length of time in order to obtain sustained clinical effects.

4. The theoretical significance of the lowered serum albumin is discussed in relation to prevailing concepts of interstitial edema in diseases other than poliomyelitis, and is applied hypothetically to central nervous system edema and the reversible paralytic factor in the acute phase of human poliomyelitis.

5. A therapeutic opinion is presented for consideration. It requires additional evaluation.

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STUDIES ON EFFUSIONS. I. GLUCURONIDASE AND LACTIC ACID IN NEOPLASTIC EFFUSIONS OF PLEURA AND PERITONEUM*

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The biochemical study of effusions is of interest chiefly for these reasons: 1, it may present the most convenient means for the detection and study of the chemical constituents and metabolites of the tumor in the living patient; 2, it may provide information leading to the discovery of new biochemical indices of the severity of neoplasia and of the effectiveness of therapy; 3, although neoplastic effusions tend to occur in late stages of the disease, their cause often remains a difficult diagnostic problem and new criteria for determining the etiology of effusions are therefore highly desirable.

Lactic acid has been generally recognized as a substance which is markedly increased in tumors as compared with normal tissues[1,10]. β–glucuronidase is one of the few enzyme systems which show increased activity in tumor tissues[2,3,4]. The cytological technique often serves to confirm the diagnosis of neoplastic exudate by the demonstration of tumor cells in effusions[8].

In the present study, the determination of lactic acid, glucuronidase and cytological examinations were done in 169 effusion fluids taken from 56 patients and the findings have been correlated with clinical and pathological information.

It appears that the neoplastic effusions are frequently but not always rich in glucuronidase, lactic acid and cancer cells, and that these components are absent (cancer cells) or low (glucuronidase, lactic acid) in non-neoplastic effusions and neoplastic transudates. In the course of the disease all 3, or any 1, of these indices may change in either direction.

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Methods. All the patients studied were hospitalized† and complete clinical studies were made of them before their inclusion in this series. Autopsies were done in as many cases as possible. Some patients were receiving chemotherapy. Chest and abdominal fluids were obtained by conventional thoracocenthesis and paracenthesis, a portion of the fluids being preserved in sodium fluoride for lactic acid and glucose analysis. Another aliquot was taken without preservative for immediate determination of glucuronidase activity and for cytological study. In some instances a modified Wright stain, described elsewhere[9], was employed. Whenever possible, repeated paracenthesis and thoracocenthesis were performed on individual patients.

The following chemical methods were used:

1. β-glucuronidase was determined according to Fishman, Springer and Brunetti[5] on the uncentrifuged specimen. The supernatant after sedimentation and the laked cell sediment were studied for glucuronidase activity. The data will be expressed for convenience in terms of the uncentrifuged specimen only.

2. Lactic acid was analyzed according to Markus[7]. Qualitative lactic acid estimations were done by Kelling's ferrous chloride test[6] using an arbitrary scale of 1+ to 3+ to indicate the intensity of the color reaction.

3. Glucose analyses were performed on zinc hydroxide blood protein-free filtrates by the Folin-Wu method.

FIG. 1.–Summary of data on patients with and without cancer.

† We are indebted to the chiefs of the medical services of the West Roxbury Veterans Hospital, the New England Hospital for Women and Children, the Faulkner Hospital, the Boston University and Tufts Services of the Boston City Hospital, for having given us access to some of their material and records.

4. Total protein was determined by digestion and Nesslerization.

5. Specific gravity was estimated with a urinometer.

Results. 1. *β–glucuronidase, lactic acid and cytology in effusions* (See Fig. 1). In 8 cases, 6 of ascites and 2 of pleural effusions caused by liver disease and cardiac decompensation, the glucuronidase activity ranged from 53 to 393 units per 100 ml. The lactic acid concentration ranged from 12 to 42.5 mg. per ml. Most specimens contained no cells and occasional mesothelial cells were seen in some.

2. *Results of Studies Repeated in the Same Patient.* A large number of repeat determinations were done in many cases. One interesting case illustrates the spontaneous changes which may occur in the body fluid. Thus, positive findings obtained at the beginning approached "normal" values toward the end (Fig. 2).

3. *Studies of Total Protein Content and Specific Gravity of Fluids.* The total protein values, as well as the values for specific gravity, were obtained but titative measurements of lactic acid offered no correlation.

TABLE 1.—RELATION OF SITE OF CANCER TO FLUID GLUCURONIDASE AND LACTIC ACID VALUES

	Glucuronidase			*Lactic Acid*		
Site of Cancer	*No. of Analyses*	*Mean*	*Range*	*No. of Analyses*	*Mean*	*Range*
CANCER GROUP						
Breast	14	655	230–2725	12	37.5	3–78
Uterus	9	435	91–611	9	61.0	6–109
Lung	17	1655	160–8000	14	78.9	15–140
Gastro-intestinal tract	35	347	122–2105	29	31.4	11–62
Ovary	23	1187	262–3960	15	50.2	15–198
Miscellaneous	7	302	164–495	5	35.0	23–54
NON-CANCER GROUP	10	206	95–393	9	24.2	11–42

In 40 cases of cancer, the glucuronidase activity in 106 determinations ranged from 0 (in one instance) to 8250 units per 100 ml. The ranges and averages in various types of cancer are given in Table 1.

The lactic acid values in the same group are also listed in Table 1 and Fig. 1 shows the distributions of lactic acid and glucuronidase values in both pleural and ascitic fluids and their relation to cytology.

In 96 fluids from cancer patients, additional qualitative lactic acid tests were performed; the relationship between the results of this test and quan- have been found not to contribute greatly to the present study.

Discussion. The results of this study showed that in many specimens taken from effusions caused by cancer the glucuronidase activity and the concentration of lactic acid were significantly elevated.

Repeated studies on the same patient showed the transition of an exudate of this type into an effusion containing little or none of these tumor metabolites and vice versa. By the usual characteristics of total protein and specific gravity, which may not change simultaneously, such effusions would still

be considered exudates. In terms of the tumor metabolites studied, however, they have changed completely and should be considered an entirely different type of effusion. It seems likely that such fluids which are devoid of the tumor metabolites studied here have no direct contact with the tumor mass and are probably caused by compression of major vessels by the tumor, a mechanism commonly believed to result in transudates. The inflammatory process often surrounding neoplastic masses may well be alone responsible for the persistence of high protein concentrations in such fluids. Functionally, this situation is quite different from that which prevails when tumor tissue infiltrating pleura or peritoneum provokes exudation with which it remains in intimate contact.

The recognition of these factors gives a reasonable interpretation of our data.

High glucuronidase and elevated lactic acid levels can occur only if there is reasonably intimate contact between a tumor and the fluid studied. Cells may or may not desquamate into such fluids and the extent of desquamation may vary.

One may assume that enclosed effusions in close contact with tumors would present a favorable medium for the study of tumor metabolites in the living patient. Our data show that disappointments would be encountered if work were to be done on effusions taken at random from patients with proven cancer. In a good number of cases of proven cancer, neither cytological findings (45 out of 106), nor glucuronidase (13 out of 106), nor lactic acid (13 out of 106) were above the average found in the control group of patients without cancer.

We believe that if any 2 of the 3 characteristics studied in this paper were to be found elevated in a fluid, the chances would be excellent that the presence of other metabolites, if present in the tumor, could also be detected in the fluid. It is to be antici-

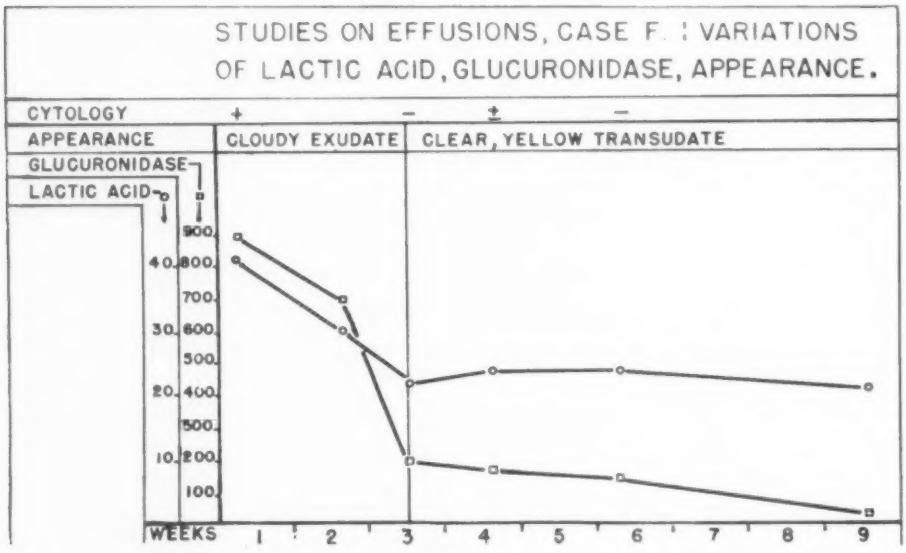

FIG. 2.—A spontaneous change *in vivo* of the chemical and cytological characteristics of ascitic fluid.

pated, of course, that there may be factors in such fluids which may neutralize or antagonize metabolites which might be studied.

In terms of clinical experience, we may state that the elevation of both chemical characteristics (glucuronidase and lactic acid) appears to be of itself diagnostic for the presence of cancer, whereas the absence of elevations and negative cytological results have no significance for the ruling out of cancer.

Summary and Conclusions. 1. In 106 aliquots of effusions from 40 patients with cancer and in 9 samples of transudate from 8 patients with liver and, or, heart disease, determinations were made of β—glucuronidase activity, lactic acid content and cytological studies were done.

2. Lactic acid values and glucuronidase activity in the controls were within narrow ranges, and no false positive cytological findings were found in these fluids.

3. There were 45 specimens of proven cancer where cytological studies were negative. In 28 of these the glucuronidase activity was above the "normal" average. The lactic acid concentration was more than in the control average in 16 of these 36 cases. In 13 fluids from patients with known cancer, none of the characteristics was elevated. The qualitative test for lactic acid was found to be unspecific and useless.

4. On repeated study in 1 patient, 1 or more of these characteristics may increase or decrease during the course of the disease and sometimes without any apparent correlation with its clinical severity.

5. Positive cytological findings alone are not always accompanied by an elevated concentration of the metabolites (lactic acid and glucuronidase) and their elevation is not invariably accompanied by the presence of detectable tumor cells.

6. It is thought probable that the presence in a high degree of all 3 characteristics indicates favorable conditions in the effusion fluid for the study *in vivo* of other tumor metabolites. If either glucuronidase or lactic acid or both should be elevated, even in the absence of positive cytological results, such findings may be of help in establishing the diagnosis.

7. Some mechanisms which may explain the variability of the composition of neoplastic effusions have been considered.

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THE SALT DEPLETION SYNDROME FOLLOWING MERCURIAL DIURESIS IN ELDERLY PERSONS

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Although the occasional occurrence of salt depletion and dehydration reactions following mercurial therapy has been recognized for a number of years, the emphasis recently placed by Gold and his co-workers[12] on intensive, daily administration in congestive failure has made the question of safety in employing this drug an urgent one[20]. The merits of daily mercurial injections in selected patients are undeniable but we have been impressed by the number of reactions in older patients. Young persons, particularly those with rheumatic heart disease, not uncommonly receive hundreds of injections over many years without serious reaction[11,22]. However, particularly in the elderly age groups, diuresis may be followed by asthenia, apathy, somnolence or restlessness, anorexia, confusion, disorientation, drop in blood pressure, fever, stupor, coma and even death. The blood urea rises and the chlorides fall. This may be true even of injections given at intervals of several days. It should be remembered that in older persons some degree of renal impairment is usually present even before the specific gravity of the urine is fixed. Poll and Stern[25] warned of dangerous dehydration reactions in the presence of old age, arteriosclerosis and cachexia. Klinghoffer[19] noted 3 instances of serious dehydration with 1 death from mercurials within 1 year on a single hospital ward. Salt depletion and dehydration reactions were found to complicate mercurial therapy, particularly in hot weather[1]. Recently Soloff and Zatuchni[29] saw 4 instances within 1 month in which dehydration following mercurial therapy contributed to the death of patients in congestive failure. Schroeder[28] has recently described the "low salt syndrome" in various conditions.

A number of warnings have been leveled against the use of mercurials in the presence of renal damage. Boone[4] described a remarkably high incidence of death among patients with renal disease and congestive heart failure who had received salyrgan. The incidence of azotemia and uremia in patients with hypertensive and arteriosclerotic heart disease has been reported twice as great following mercurial diuresis as in those who had not received injections[16]. Fishberg[9] avoids mercurials if the maximum urine concentration is not greater than 1.015. DeGraff and Nadler[8] emphasized the fact that patients with renal damage furnish the largest group with fatal reactions following mercurial diuresis. Ray and Burch[26] believe that acute glomerulonephritis, renal insufficiency, blood urea nitrogen greater than 60 mg. per 100 cc., oliguria, hematuria

and severe albuminuria in patients with previously normal urine contraindicate the use of mercurial diuretics.

Much less common than dehydration reactions following mercurials is renal injury. The transitory appearance of albumin, casts, red and white cells in the urine is not rare[6,30]. Anuria due to renal necrosis and toxic nephrosis has been reported[23,31].

Another cause of oliguria and uremia following mercurial diuresis is swelling of the prostate in persons with prostatism, active or latent[34]. This may prove a serious complication.

Although they do not fall directly within the province of this paper, the fatal reactions to intravenous mercury injections[7,17,24] and the sensitivity reactions of chills, fever, urticaria and asthma may be mentioned[10,13].

The incidence of salt depletion and dehydration reactions and renal injury following mercurial diuretics undoubtedly is related to the frequency of injections, the selection of cases and the use of low salt diets.

The following case histories have been chosen from patients observed by the authors during the past 2 years. This study does not constitute a statistical analysis. It is our impression that the incidence has increased since the introduction of intensive, daily mercurial therapy. Two of the cases cited below occurred within a period of 4 weeks on one hospital ward where it had become the rule to administer daily mercurials.

Case Presentations. CASE 1. A.K., 578682, male, aged 70, was admitted to the hospital in congestive heart failure. He had received mercurial injections every week or two over a period of 4 years. The heart was enlarged, auricular fibrillation was present and there was edema of the ankles and sacral area. The blood pressure was 170/72 mm. Hg. The blood urea nitrogen was 15 mg. per 100 ml., the urea clearance was 54% in 2 hours, the phenolsulfonephthalein excretion was 35% and the specific gravity of the urine was 1.020. He was given 2 ml. mercupurin intravenously daily for 10 days. At the end of that time he had lost 17 lbs. and the signs of failure had disappeared; however, the urea nitrogen was 57 mg. per 100 ml., the sp. gr. of the urine was 1.016 and the phenolsulfonephthalein excretion was only 28%. Twelve days later the urea nitrogen had risen to 67 mg. per 100 ml. and the sp. gr. of the urine was 1.012. The patient became hyperpneic, lethargic and disoriented, he vomited and developed a tremor of the hands. The urinary output fell to 85 ml. in 24 hours and the urea nitrogen rose to 109 mg. per 100 ml. The blood chlorides were 679 mg. per 100 ml. He received glucose in saline intravenously each day but became comatose and died 16 days after the cessation of mercurial therapy. Postmortem examination was not allowed.

CASE 2. W.W., 596140, male, aged 75, developed acute posterior wall infarction with congestive heart failure and auricular fibrillation with rapid ventricular rate. There were numerous rales at both bases, gallop rhythm and edema of both ankles. The liver was palpable 3 cm. below the costal margin. The blood urea nitrogen was 38 mg. per 100 ml. He was given digitoxin and quinidine, and the rhythm became regular. He received 2 ml. of mercuhydrin by muscle daily for 6 days. Singultus developed soon after admission and became progressively more severe despite all known therapeutic measures, including phrenic nerve block. On the sixth day of mercurial therapy the urea nitrogen was 66 mg. per 100 ml., the blood chlorides 556 mg. per 100 ml., and the CO_2 combining power 69 vol. %. He became drowsy, confused, disoriented and restless. Muscle twitching set in. Thereafter he gradually improved. On the 12th hospital day the blood urea nitrogen had fallen to 45 mg. per 100 ml. and the blood chlorides to 500 mg. per 100 ml., but the degree of congestive failure increased and after 2 weeks he suddenly died. Post mortem examination was not obtained.

CASE 3. E.E., 576574, male, aged 76, entered the hospital with acute urinary retention due to prostatic hypertrophy. He had noticed increasing dyspnea and edema during the previous 3 months. Examination revealed severe congestive failure. His neck veins were distended and numerous moist rales were present at both bases. The heart was enlarged to the left and the rate was 36 as a result of complete A-V block, indicated by electrocardiogram. The liver was palpable 5 cm. below the costal margin and was firm and nodular. Severe edema was present. The blood urea nitrogen was 19 mg.

per 100 ml. He was placed on a 1000 calorie diet, containing only 200 mg. of sodium, and fluids to 3000 cc. He received 1 cc. of mercuhydrin daily by vein for 11 days. By the 4th day he had lost 16 lbs., the liver and edema had receded and the blood urea nitrogen had risen to 32 mg. per 100 ml. Three days later he became asthenic, somnolent, confused and disoriented. The left arm and leg twitched. Cheyne-Stokes respiration developed. He was given 0.8 mg. of digitoxin which caused vomiting. On the 16th day the blood urea nitrogen rose to 49 mg. per 100 ml. and the chlorides fell to 468 mg. per 100 ml.; the CO_2 combining power was reduced to 35.6 vol. %. A regular diet with salt was prescribed, the patient became alert, and the blood chemistry figures gradually returned to normal. Transurethral resection was performed and the patient was discharged improved.

Case 4. M.S., male, aged 57, entered the hospital because of progressive dyspnea and orthopnea. On admission his blood pressure was 260/140 mm. Hg. The heart was enlarged to the left, and gallop rhythm was present. There were numerous rales at both bases, the liver was palpable 5 cm. below the costal margin and moderate edema of the ankles was present. The blood urea nitrogen was 20 mg. per 100 ml. He received 2 ml. of mercuhydrin daily for 2 days, then 2 ml. twice daily for 2 days, then 2 ml. daily for 3 days, a total of 18 ml. in one week. On the 4th day, the blood urea nitrogen was 32 mg. per 100 ml., the chlorides 575 mg. per 100 ml. and the CO_2 combining power 67 vol. %. Three days after the cessation of the injections, the urea nitrogen had risen to 51 mg. per 100 ml., the chlorides and CO_2 were essentially the same. At this time he had lost 20 pounds. The venous pressure and circulation time were normal. Phenolsulfonephthalein excretion was 30%. There were occasional rales at the bases, the liver was still palpable and a small pleural effusion was present on the right side. The blood urea nitrogen fell to 24 mg. per 100 ml. and the chlorides to 550 mg. per 100 ml. At this time, the patient became paranoid, confused and uncooperative, refusing nourishment and medication. He received 500 ml. of normal saline solution by clysis, and the following day these symptoms had disappeared. He improved steadily and the urea nitrogen fell to 16 mg. per 100 ml.

Case 5. 572970, female, aged 73, was admitted in congestive failure of several months' duration. Rales were present at both bases. The heart was markedly enlarged to the left, auricular fibrillation was present and there was a rough systolic murmur over to the precordium. Her blood pressure was 220/120 mm. Hg. The blood urea nitrogen was 19 mg. per 100 ml. The venous pressure was 19.5 cm. H_2O, rising to 25 cm. on RUQ pressure. She was given a low salt diet, fluids to 3000 ml. and digitalis. Two ml. of a mercurial were given twice weekly. After the 5th injection the patient had lost 7 pounds. The blood urea nitrogen had risen to 40 mg. per 100 ml. and therefore the injections were stopped. Nevertheless, the patient became weak, nauseated, somnolent and confused. Two weeks later the blood urea had risen to 89 mg. per 100 ml. and the CO_2 combining power was reduced to 27 vol. %. The blood chlorides were 673 mg. per 100 ml. Intravenous glucose in saline and 1/6 M lactate were given, the patient's symptoms rapidly disappeared and the urea nitrogen gradually fell to 20 mg. per 100 ml.

Case 6. B.H., male, aged 73, with longstanding hypertension, marked cardiac enlargement and left bundle branch block, entered the hospital in advanced congestive failure with extensive bilateral pleural effusion, ascites and massive edema. His blood urea nitrogen was 23 mg. per 100 ml. He received 2 daily injections of 2 ml. of mercurial with profuse diuresis and diminution of edema; however, the pleural and peritoneal collections of fluid persisted; 1000 ml. were then withdrawn from the right pleural cavity and 6000 ml. from the peritoneal. He received 1 ml. of mercury for 2 days, but these were discontinued because he had become apathetic, stuporous and disoriented. At this point the blood urea had risen to 54 mg. per 100 ml. and the chlorides had fallen to 515 mg. per 100 ml. He improved and the urea fell to 28 mg. per 100 ml. One week later the mercurial injections had to be renewed, 1 ml. being given every few days. Death occurred 1 month later.

Case 7. A.C., female, aged 69, entered because of dyspnea and cough of 6 months' duration. There were rales at both bases, the heart enlarged to the left and auricular fibrillation was present. The liver was palpable 5 cm. below the costal margin. There was no edema. She was given mercupurin 2 ml. every 5 days. After 3 or 4 doses the signs of congestive failure had receded but she complained of being very weak and became drowsy. The injections were discontinued. The blood urea nitrogen proved to be 120 mg. per 100 ml. She was directed

to take fluids liberally, and soon improved. The blood urea nitrogen fell to 43 mg. per 100 ml.

CASE 8. A.S., male, aged 81, was observed in advanced congestive failure. He had received 2 ml. of mercuhydrin daily for 5 doses; nevertheless, a large right pleural effusion was present, the liver was felt below the level of the umbilicus, and considerable edema was present. Thoracentesis yielded 1600 ml. of fluid. His condition improved; the liver was no longer palpable following 2 additional doses of mercuhydrin. However, 2 days later, he became irrational, disoriented and uncooperative. He was given salt by mouth but died after several days in pulmonary edema. This case emphasizes the caution required in treating even advanced congestive failure with mercurials in elderly persons, and the difficulty of combating salt depletion in such persons.

Discussion. Profound electrolyte imbalance may follow mercurial diuresis. Blumgart and his colleagues[2] demonstrated that sodium, potassium, calcium and chlorides, in addition to water, are excreted in increased amounts. Numerous recent investigations have emphasized the greater excretion of sodium following mercurial diuretics, especially with unrestricted sodium intake[14,18,27]. Poll and Stern[25] compared the marked asthenia, restlessness and muscular cramps following massive mercurial diuresis to Addison's disease. Patients with chronic glomerulonephritis with preponderant salt loss have a similar asthenia[33]. These symptoms may be attributed to the loss of sodium chloride. Another factor contributing to asthenia may be the loss of potassium. Urinary loss is one of the important routes for potassium excretion[32]. With such large quantities of fluid excreted during intensive diuresis, the possibility of potassium depletion must be considered very real.

Elevation of blood urea nitrogen was present in all our cases. A rise in blood urea nitrogen may be produced by diminished glomerular filtration and nitrogen or water imbalance. The exact mechanism which obtains in mercurial diuresis is obscure but it may be related to some initial renal involvement. Dehydration reduces the urea clearance with elevation of blood urea even in normal subjects[21]. In most cases the elevation of blood urea nitrogen following diuresis is reversible but in the presence of renal damage it may persist. Binger and Keith[3] found signs of persistent renal impairment after massive diuresis in 16% of their patients. In any event, a rising blood urea nitrogen may be an ominous sign and should be carefully looked for. The blood urea should be determined at least twice a week and the blood sodium or chlorides and CO_2 combining power occasionally. Sometimes the only warning of approaching difficulty is a fall in blood chlorides. Unfortunately, with daily mercurial therapy, the full-blown syndrome of salt depletion and dehydration or, rarely, toxic nephrosis, may occur so suddenly and precipitously that the laboratory data serve only to confirm, not to warn. This may occur even in the most rigidly observed cases where the blood urea nitrogen is determined every other day.

Salt depletion and dehydration reactions do not occur so frequently in young patients with rheumatic heart disease as in elderly arteriosclerotic or hypertensive patients. Certainly in the latter, dehydration and salt depletion are of dire prognostic significance and may contribute directly to a fatal outcome. This is doubtless the result of the presence of unrecognized renal damage in the elderly group. Another factor in producing symptoms probably is the marginal status of the cerebral blood flow in elderly patients with arteriosclerotic and hypertensive cardiovascular disease. The symptoms seen in dehydration reactions, *i.e.*, somnolence, confusion, disorientation, restlessness, stupor, are cerebral symptoms.

Dehydration further compromises an already impaired cerebral blood flow. Whereas these symptoms occur not infrequently, even with conservative mercurial therapy, it is obvious that their likelihood is considerably increased by intensive treatment. Prevention of such reactions is difficult although frequent determinations of blood urea nitrogen and sodium will keep them at a minimum. The recent introduction of thiomerin[15], a mercurial given by subcutaneous injection, promises to be of aid in reducing these reactions.

This does not imply that daily mercurial therapy does not have its place in the treatment of congestive failure. In our experience it is an excellent therapeutic tool but it is strenuous. In elderly hypertensive and arteriosclerotic patients, daily injections may be dangerous and should be used with great caution, if at all. This holds particularly when there is any indication of prostatic enlargement.

It is usually possible to restore renal function and electrolyte balance by administering salt and fluids. This may be done orally or by injection of concentrated saline solution, that is, 5%[28]. The latter has been administered even in the presence of congestive failure, as evidenced by edema, enlargement of the liver and pulmonary congestion[28].

Summary. Attention is directed to the occurrence of salt depletion and dehydration reactions following mercurial diuresis in elderly persons. These reactions may be fatal.

The frequency of such reactions appears to have increased following the introduction of intensive, daily mercurial therapy.

In elderly persons the dose should be 1 ml. given at intervals of several days. The blood urea nitrogen should be determined twice a week.

Mercurial diuresis may induce symptoms of prostatism.

Salt depletion reactions usually respond to the administration of salt.

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MYASTHENIA GRAVIS

Some Observations on the Effects of Various Therapeutic Agents, Including Thymectomy and ACTH in a Nine Year Old Child.

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AND

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Myasthenia Gravis is rarely encountered in infants and children[4,12,13,19,20,22,23,24,30,40]. The prognosis is generally poor despite the use of a large variety of medicinal agents as well as thymectomy and Roentgen-rays.

The case herein detailed is being reported, therefore, not only because we wish to document still another instance of myasthenia gravis in a child, but also to record certain observations made relative to the effect of thymectomy and ACTH (pituitary adrenocorticotropic hormone) in this disease.

Case Report. C.S., a 9 year old white girl, was first admitted to this department on March 26, 1949, because of impaired articulation and generalized fatigue. Two months prior to admission, psychiatric aid was requested, because of an altered expression of smiling and increasing difficulty in phonation and articulation. Subsequently she tired readily, became irritable and developed bilateral partial ptosis. Mastication and swallowing were accomplished with great effort. Her past medical and family history were noncontributory.

Physical examination revealed a pallid child of normal weight and height with partial ptosis of both eyelids, a wan, weak smile and hesitant, lisping, low-pitched speech. A fatigued demeanor followed any maneuver which required muscular effort. She was noncomplaining, pleasant and appeared to be an exceedingly well integrated child. The thyroid, although not unduly enlarged, was visible and palpable. There was weakness of the masseter muscles and associated muscles of mastication with bilateral weakness of muscles innervated by the seventh cranial nerves. The gag reflex was intact but weakness of the constrictor muscles of the pharynx was evident. She could stand on her heels or toes but had difficulty in balancing on one leg. All other physical findings were negative.

Laboratory studies revealed normal urinalysis, hemogram, blood sugar, blood urea nitrogen, sedimentation rate and serum tests. The cholesterol and cholesterol esters measured 290 mg. and 180 mg. per 100 cc. of serum respectively. Two estimations of 24 hour urinary excretion of uric acid and creatinine were normal. Nose and throat cultures were negative for *C. diphtheriae*. Lumbar puncture revealed clear fluid, under normal pressure; microscopy was negative. The protein content was 25 mg. per 100 cc. of cerebrospinal fluid, the globulin was not increased and the Wassermann and colloidal gold tests were negative. Roentgenographic studies of the chest in various exposures and by means of planographic studies revealed no evidence of thymic enlargement or tumor. Swallowing function was normal on fluoroscopic examination.

Muscular function was temporarily improved after a test dose of prostigmine. The daily oral maintenance dose of this drug and of ephedrine sulphate was established at 7.5 mg. each, every 3 hours. The child was discharged April 24, 1949, in satisfactory condition.

On April 29, 1949, the patient was readmitted to the hospital because of recurrence of symptoms. Examination revealed coarse and sibilant rhonchi throughout the chest and a temperature of 101° F. Ptosis of the eyelids, although bilateral, was worse on the left. Prostigmine 0.5 mg. and atropine 0.45 mg.

hypodermically, every 6 hours alleviated symptoms.

An exploratory mediastinotomy and thymectomy was done on May 4, 1949, by Dr. Herbert H. Hawthorne. The removed thymus weighed 12 gm. One lobe measured 6 x 3 x 1 cm. and the other measured 5.4 x 3 x 1 cm. Microscopic examination revealed the cortex to be composed of large, homogeneous islands of small lymphocytes with some increase in thickness of the fibrous trabeculae. The medulla had a pleomorphic appearance. Lymphocytes intermingled with slightly less abundant reticuloendothelial cells and a number of tissue eosinophils. Many Hassall bodies stained poorly and some of these were frankly hyalinized and showed early calcification. Scattered through the medulla were occasional well organized follicles with large germinal centers.

The patient's immediate postoperative clinical course was uneventful. Remission of symptoms was maintained by 0.5 mg. of prostigmine and 0.45 mg. of atropine, hypodermically, every 6 hours. On May 12, 1949, she developed fever, tachycardia and cyanosis. This was attributed to atelectatic pneumonia of the right lower lobe due to aspiration of food and inability to expectorate bronchial secretions. Pooling of secretions in the pharynx was troublesome. Her condition became progressively worse and she was placed in a respirator. Articulation and swallowing were markedly aggravated. This crisis was overcome by postural and bronchoscopic drainage, oxygen by nasal catheter, parenteral fluids, prostigmine, hypodermically and intravenously, atropine sulphate, penicillin, epinephrine and ephedrine sulfate intramuscularly.

On May 15, 1949, when she was no longer dependent on the respirator, she was, at this time, receiving 1.5 mg. of prostigmine methylsulfate every 3 hours. Intramuscular injections of aqueous adrenal cortical extract (Upjohn), 5 cc. twice daily, and crude liver extract, 1 cc. daily, were started on June 2, 1949. She was now able to leave her bed for short periods. On June 4, the 24 hour urinary uric acid-creatine ratio was 1.5:1 and on June 15, the blood serum sodium estimation was 141 mEq./L.; the potassium was 4 mEq./L.

Symptoms again recurred on June 27, 1949, requiring re-administration of the program employed during the previous relapse. Two days later, after a transfusion of 500 cc. of citrated whole blood, she improved noticeably and was removed from the respirator.

On July 7, 1949, 10 mg. of ACTH* was administered intramuscularly. This was preceded and followed 4 hours later by total eosinophil counts. The eosinophils dropped from 169 to 59 cells per c.mm. On July 11, 1949, ACTH was started in a dose of 10 mg. every 6 hours and continued for 5 days. During this period prostigmine had to be continued in order to control symptoms. No objective or subjective improvement was discerned during this period of ACTH therapy.

The effects of ACTH were noted on the formed elements of the blood (Table 1), serum uric acid and creatinine concentration (Table 2), urinary excretion of urie acid and creatinine (Table 3), and the electrocardiogram.

As may be seen Tables 1, 2 and 3, after the administration of ACTH the total white blood cells and neutrophils increased, lymphocytes decreased, uric acid content of the serum and urinary uric acid excretion increased, serum creatinine concentration decreased and urinary creatinine excretion increased. These observations are in general agreement with those made by others[17,33]. In contrast with the fall noted after the test dose, the total eosinophil count showed no remarkable change during the period of therapeutic administration of ACTH.

Figs. 2 and 3 show electrocardiograms done with the patient in the upright and supine positions, prior to the injection of 1 mg. of prostigmine when muscle weakness was marked and dysphagia and ptosis present, and 15 minutes afterwards when clinical improvement was noticeable.

It is difficult to interpret the electrocardiographic changes because of the rather frequent alterations in the control electrocardiograms, particularly with respect to the T waves and ST segments. However, the configuration of the ST segments and the prolongation of the QT intervals in CR2 and CR3 may represent the result of some degree of hypopotassemia following ACTH.

The effect of posture on the electrocardiogram is shown in Fig. 2. There are marked T wave and ST segment changes in the standing position which revert to normal in the recumbent position. These changes are characteristic of the so-called unstable T waves which have been described by Wendkos, Logan and others, and attributed by them to diminution in sympathetic tone. After prostigmine (Fig. 3a) the T wave in the standing position was less inverted in Lead 2 and was fairly upright in CR2 as compared to the tracing before prostigmine (Fig. 2a). This

* Kindly supplied by John R. Mote, M.D., Armour Laboratories.

TABLE 1.—EFFECT OF ACTH ON THE BLOOD.

		ACTH	
Date	6–27–49	7–11–49 to 7–12–49	7–15–49 to 7–13–49
R.B.C.	4,130,000	4,970,000	4,440,000
Hb.	12 G. 72%	14 G. 87%	13 G. 78%
W.B.C.	7,200	8,300	12,000
Neutrophils	3,456 (48%)	5,229 (63%)	9,075 (75%)
Lymphocytes	3,312 (46%)	2,573 (31%)	2,662 (22%)
Monocytes	288 (4%)	166 (2%)	
Eosinophils	144 (2%)	332 (4%)	363 (3%)

TABLE 2.—EFFECT OF ACTH ON SERUM URIC ACID AND CREATININE CONCENTRATION.

		ACTH			
Date	(Normal)	6–27–49	7–11–49 to 6–30–49	7–15–49 to 7–12–49	7–15–49
Serum Uric Acid (mg.%)	2.0–5.0	3.2		3.3	4.0
Serum Creatinine (mg.%)	0.3–1.3	2.4	3.9	1.9	1.8

TABLE 3.—EFFECT OF ACTH ON URINARY EXCRETION OF URIC ACID AND CREATININE.

		ACTH		
Date	6–4–49	7–11–49 to 7–15–49 7–11–49	7–13–49	7–16–49
		24 Hour Urinary Excretion		
Uric Acid (mg./L.)	670	652	689	750
Creatinine (mg./L.)	455	580	900	466

FIG. 1. A.—Control (5/31/49). Note upright T waves of low amplitude in Leads 1 and 2, inverted T waves in CR2 and CR3, and upright T waves in CR4 and CR5.

(In this and the following records, the first 3 strips are from the usual limb leads, the last 4 from chest leads.)

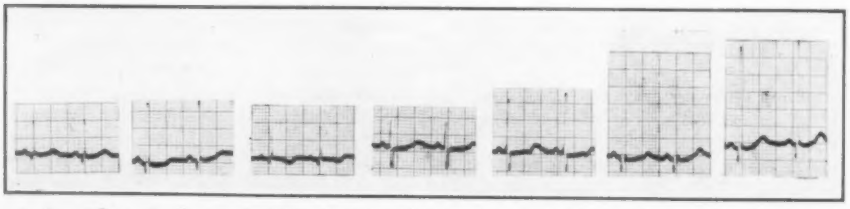

FIG. 1. B.—After 2 days of ACTH (7/13/49). Note ST depression in Lead 2 and in precordial leads accompanied by lengthening of the QT interval, particularly marked in CR2 and CR3.

may be due to the parasympathomimetic action of prostigmine. The improvement in the T waves observed in Fig. 3b is similar to that observed in Fig. 2b. In this tracing there is a summation of the normalizing effects of both prostigmine and the recumbent posture.

Stigminene bromide (1-benzyl-3-(dimethylcarbamyloxy)-pyridinium bromide), a choline esterase inhibitor, was also employed but proved inferior to prostigmine in relieving clinical symptoms when given in doses of 1.0 mg. hypodermically. In September the patient became more listless, weaker and failed to respond to prostiginine methylsulfate (1 mg.) every 2 hours. Benzedrine sulfate 5 mg. 3 times daily likewise was without beneficial effect. A steady downward clinical course ensued. She was placed in the respirator on September 22, 1949. Typical myasthenic facies and generalized muscular weakness, particularly of the muscles of mastication, deglutition and respiration developed. Lethargy increased until she died on September 24, 1949.

Autopsy (Dr. Karl J. Myers, 2½ hours

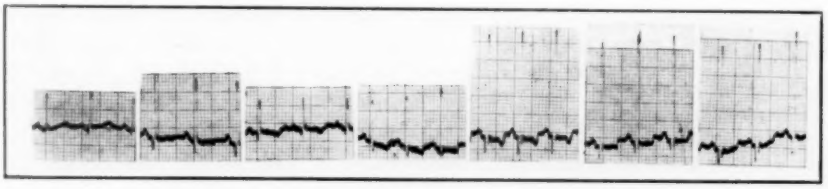

Fig. 2. A.—Before prostigmine, standing (9/15/49). Note low amplitude T wave in Lead 1, inverted T waves in CR2, CR3 and CR4 with depression of the ST segment in CR5.

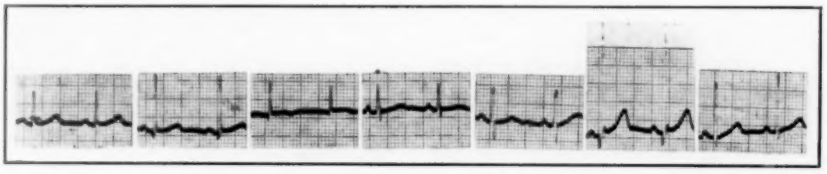

Fig. 2. B.—Before prostigmine, supine (9/15/49). Note increased amplitude of T wave in Lead 1 with upright T wave in Lead 2. T waves are now upright in all precordial leads.

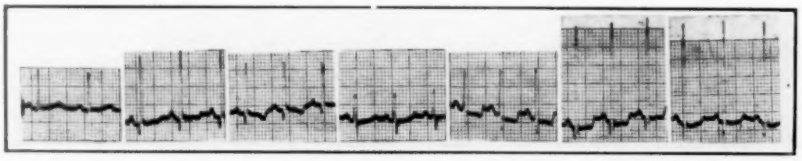

Fig. 3. A.—Fifteen minutes after prostigmine, standing. Note low amplitude T1, depressed ST2, inverted T3. The T wave in CR2 is upright. The T wave is inverted in CR3 and CR4 and the ST segment is depressed in CR5.

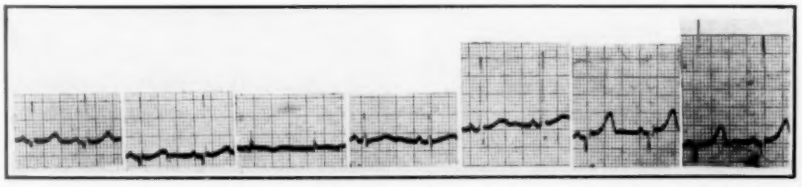

Fig. 3. B.—After prostigmine, supine. Note increased amplitude of T1. T2 is now upright and the T waves are now upright in all the precordial leads.

after death). Widespread broncho-pneumonia and an intussusception (5 cm. in length) in the jejunum, 10 cm. from the ligament of Treitz. The intussusception was not fixed or discolored and suggested either a terminal agonal phenomenon or the result of prostigmine. The brain could not be examined. The other organs appeared normal.

Microscopic Examination. Sections from the rectus abdominis, pectoralis major, ileopsoas and diaphragm demonstrated no lymphorrhagia; some of the muscle fibres were atrophic with loss of cross striations. The heart muscle showed some tendency to enlargement of the nuclei. In the lymph nodes slight increase in cellularity without reticulo-endothelial proliferation of the follicles was seen. The thyroid acini, although large, were within limits of normal and well filled with colloid. In the adrenals, the medullary tissue was abundant but the cortical cells revealed decreased vacuolization possibly due to lipoid depletion.

Discussion. The etiology of myasthenia gravis is not definitely known. Pathognomonic lesions and basic abnormal functions have not been proven for the disease. Weakness of striated muscle, the chief characteristic of myasthenia gravis, has been attributed to an imbalance at the myoneural junction of an enzyme system involving acetylcholine and choline esterase, and specifically to a deficiency of the former substance. Acetylcholine activity may be decreased by deficient formation, neutralization by an antagonistic substance or by increased activity of choline esterase. Choline esterase hydrolyzes and inactivates acetylcholine. There is no conclusive evidence of the modus operandi and the specific role of the acetylcholine—choline esterase system in the propagation of nerve impulses. Prostigmine is usually regarded as the drug of choice in the medical management of myasthenia gravis purportedly by its ability to inhibit choline esterase activity. Di-isopropylfluorophosphate (D. F. P.) is more effective than prostigmine in reducing the plasma choline esterase but has less therapeutic effect in myasthenia gravis than does prostigmine[7].

The thymus was first implicated in the disease by Weigert[37] in 1901. The theory that symptoms of muscular weakness in myasthenia gravis is due to blocking of conduction from the motor nerves to muscles by a thymic factor has had added support from recent investigations. McEachern[25] suggested that the thymus inhibits muscular contraction. It has been demonstrated that saline extracts of either normal thymus or surgical and postmortem myasthenic thymus significantly reduce the neuro-muscular response to stimuli[5]. Thymic extracts and serum of patients with myasthenia gravis inhibit the synthesis of acetylcholine[34,36]. Blalock[3] observed that thymectomy often cured or improved the patient with myasthenia gravis. Keynes[21] reported thymectomies in 2 girls, 4½ and 2½ years of age respectively, with a good result in the former and death 4 months after operation in the latter. At necropsy a lobe of the gland was found equal in size to the one removed at operation. Bell[2] found either thymoma or an enlarged thymus in 27 of 56 cases. Norris[27] found the thymus involved in 35 of 80 autopsied cases of myasthenia gravis. In 32 thymectomies reported by Eaton[10] 15 had thymic tumors. Of the latter, 1 died, 3 were not improved, 4 showed moderate alleviation of symptoms, and 7 were considerably improved. Of those thymectomized in the absence of tumor, 3 died, 6 were not improved, 5 showed moderate improvement, and 3 were much improved. Castleman and Norris[6], in an excellent review of 295 cases culled from the literature and 35 cases from the Massachusetts General Hospital, found that 14.5% of the cases of thymic tumor occurred before the age of 30, but none under 20. In cases of myasthenia gravis, the incidence of thymoma was most prevalent between the ages of 30 and 60, and the absence of

tumor was greatest between 15 and 35 years of age. Thymomas were found in 15% of their series. The disease was more often encountered in females up to the age of 40 years. The duration of symptoms was shorter in the group associated with tumor.

In view of the comparatively good results obtained by thymectomy[6] attempts have been made to affect the thymus in myasthenia gravis by roentgen therapy. Aring[1] treated 3 females with Roentgen-rays with inconclusive results. He suggested roentgen therapy as a therapeutic test prior to surgery.

Soffer[29] attempted a "medical thymectomy" by means of ACTH in a 29 year old female, with a thymic tumor and myasthenia gravis. Roentgenographic studies revealed a diminution in the size of the thymic tumor during the period of ACTH therapy but a return to its former size 3 weeks after cessation of treatment. During ACTH therapy no decrease in prostigmine requirements was possible and no alleviation of symptoms was discerned, but an increase in strength and well being was noted 3 to 4 days after the cessation of treatment. Prostigmine was not required 32 days after ACTH therapy was completed and no recurrence of symptoms had occurred by the time of the report. The beneficial effect of ACTH on the size of the tumor was attributed to dissolution of thymic lymphocytes in the presence of functioning adrenal glands. Torda and Wolff[35] treated 5 females with myasthenia gravis with ACTH and obtained partial remissions which had persisted for 3 months at the time of their report. They cited the ability to increase acetylcholine synthesis *in vivo*, as one of the reasons for the beneficial effect of this hormone in myasthenia gravis. However, ACTH mediates a complexity of reactions in end organs concerned with electrolyte distribution and metabolic processes which in themselves may influence neuromuscular activity.

Hellman[16] treated 5 myasthenic patients with ACTH with adverse results, possibly related to potassium diuresis or an altered intracellular and extracellular Na-K ratio. Two of Hellman's patients had temporary restoration of muscle function when treated with Compound A (11 dehydrocorticosterone), following an adverse affect from ACTH. "Metabolic" fractions of the adrenal cortex have been used in the treatment of myasthenia gravis. Soffer has demonstrated a similar but less pronounced reduction in the size of the thymic mass following the daily administration of 5 cc. of lipoadrenal cortical extract 3 times daily for 4 days. Our case showed no beneficial effect from either thymectomy, ACTH or aqueous adrenal cortical extract.

In the past, potassium salts have been employed in an attempt to relieve the manifestations of myasthenia gravis. The potassium ion was once thought to be the possible chemical mediator in the propagation of the autonomic nerve impulse[14]. It is now believed, however, that acetylcholine is liberated at the cholinergic nerve endings and that it is the chemical agent which stimulates the end organ. Linked with this process, in some as yet unknown manner, is the potassium ion. When an autonomic ganglion is perfused with a fluid containing 4 times the normal concentration of potassium, acetylcholine is liberated. The same concentration of potassium, perfused through a denervated ganglion, results in stimulation of the ganglion cells without the intervention of acetylcholine[14]. Clinically, it has been noted[5,11,15] that an extreme increase or decrease of the plasma level of potassium causes an ascending paralysis of the Landry's type. Harvey suggested that the primary defect is in the muscle itself, since

the same physiological function is disturbed by either an increase or decrease in the serum potassium level. Normally, the intracellular component of muscle contains about 80 mEq./L. of potassium per kg. and the extracellular fluid bathing the muscle fibres contains from 4 to 5 mEq./L. The ratio of these concentrations may be of importance for the normal function of muscle. If the ratio is disturbed by an altered concentration in either the intra or extracellular phase of muscle, the resulting clinical expression may be similar. Cumings[9] reported high values for the potassium content of muscles in patients with myasthenia gravis; return of muscle power and decrease in muscle potassium content followed prostigmine administration. In 1 case he demonstrated a rise in serum potassium content from 25.2 to 36.7 mg. % after prostigmine. In known cases of reduced serum potassium levels associated with paralysis[5], the palsy begins in the muscles of the extremities and trunk, while muscles innervated by the cranial nerves are not appreciably affected. This is in contrast to the involvement in myasthenia gravis where muscles innervated by cranial nerves are particularly involved.

Electrocardiographic aberrations have been infrequently reported in myasthenia gravis. White[38] stated that the disease is not accompanied by heart disease. No abnormalities were noted by Taquini, Cooke and Schwab[31] in the limb leads of the electrocardiograms in 14 cases. Katz[18], however, noted that the electrocardiogram may be abnormal in some instances and that drugs used in therapy may influence the electrocardiogram by affecting the disease rather than the heart per se. One of the common electrocardiographic changes produced experimentally in dogs by administering anti-choline esterase drugs of the long and short acting types (TEPP, HETP, physostigmine, prostigmine and DFP) was inversion of T waves in all leads[28]. The T wave is a much more unstable deflection than any other in the electrocardiogram and is more readily altered than are the others by both the position of the heart and its autonomic innervation. In Fig. 2 A, the marked T wave and ST segment change in the standing position which revert to normal in the recumbent position, demonstrate the characteristic picture of unstable T waves. In Fig. 3 A, the electrocardiogram taken in the standing position after prostigmine injection shows some improvement over that taken before prostigmine. The improvement in the T waves observed in Fig. 3 B is similar to that observed in Fig. 2 B, and is a summation of effects of both prostigmine and the recumbent posture to normalize the T waves.

Serum potassium levels are reflected in rather characteristic electrocardiographic patterns[5,26,32]. Winkler, Hoff and Smith[39] demonstrated changes in the electrocardiograms of dogs receiving various amounts of potassium chloride intravenously. There were elevations of the T wave when the serum potassium level ranged between 5 and 7 mEq./L. and cardiac arrest when the serum potassium content measured between 14 and 16 mEq./L. In Fig. 1 B, taken after 2 days of ACTH therapy, the configuration of the S-T segments and the prolongation of the QT intervals in CR2 and CR3 could have been the result of some degree of hypopotassemia conditioned either by potassium diuresis or an altered cellular and extracellular sodium-potassium ratio. It is difficult to correlate the effect of ACTH with the electrocardiographic changes because of the rather frequent alterations in our control electrocardiograms, particularly of the T waves and the S-T segments.

Summary. 1. A case of myasthenia gravis in a 9 year old girl is reported with autopsy findings.

2. In addition to thymectomy, a variety of therapeutic materials, including prostigmine, aqueous adrenal cortical extract and ACTH were tried without success.

3. The response to ACTH of the formed elements of the blood, serum creatinine and 24 hour urinary uric acid creatinine excretion was similar to that reported by others in persons with normal functioning adrenal cortices.

4. Correlation between ACTH therapy and electrocardiographic changes was not definite. However, a hypopotassemic effect was suggested.

5. Prostigmine tended to normalize T waves inverted when standing.

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FATALITIES IN SALMONELLA INFECTIONS

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The material for this study consists of 3279 human Salmonella infections with 174 fatalities. They were taken from a total of almost 5000 Salmonella cultures identified in the New York Salmonella Center during the 10 years from April 1939 to April 1949. The bacteriological, clinical, and epidemiological aspects of a part of this material until the end of 1945 have been discussed in 2 previous papers by Seligmann, Saphra, and Wasserman[6,7].

For this study all cultures derived from non-human sources (animals, food, water, sewage) were eliminated. Approximately 300 cultures of *S. typhosa* were omitted from consideration because their low incidence in the cultures received is accidental; most laboratories are in a position to diagnose *S. typhosa*, and forward only those cultures which for some reason pose a diagnostic problem. Further excluded were almost 900 cultures submitted by Army laboratories during war time. The clinical data, due to military exigencies, were mostly insufficient. The special conditions of Army life, and the social structure of the group (such as age, sex, vaccination, foreign countries) forbade generalization. Repeated cultures from the same patient were counted as one case. Also omitted were all cultures for which an adequate clinical diagnosis was missing. With all these deductions, the above mentioned 3279 Salmonella infections with 174 fatalities remained for evaluation.

Table I enumerates the 26 types involved in the fatalities. While some, (that is, SS. *typhi murium* and *cholerae suis*) show high figures, others are represented with only few fatalities, down to single cases. Among these are 2 types which generally are judged to be rather pathogenic, SS. *paratyphi B* and *panama*, which are represented by 2 and 3 fatalities in 143 and 113 infections, respectively. There was no fatality due to *S. paratyphi A*. This type is very rare in the United States; only 29 cultures have been submitted to us in 10 years, and the majority of these came from Havana. Among the rare types, *S. havana* is of particular interest and deserves some explanation. The first culture of this type was received in 1939 from Dr. A. Curbelo in Havana; it was one of numerous identical cultures isolated from feces, blood, spinal fluid, and various organs, post mortem, in an outbreak in a maternity hospital in Havana. Twenty-one newborn babies, 2 to 9 days of age, fell sick with signs of acute meningitis; all of them died[4]. Whether this terrifying event was due to the very young age of the patients, a particularly invasive variant of the type, an overwhelming infection, or a combination of these factors, has never been determined. Only a few subsequent isolations of *S. havana* have been reported: by Fulton[6] from some cases of gastroenteritis in Texas, from American-made spray egg powder in Great Britain[5], and by Hirsch[4] in Palestine from a severe gastroenteritis. None of these patients died.

While the absolute figures of fatalities and, or, isolations in 22 of the

TABLE 1.—SALMONELLA CULTURES ISOLATED FROM FATAL CASES.

(The figures in parentheses indicate the total number of cultures of the same type where adequate diagnosis was given.)

S typhi murium	63	(1155)	S. litchfield	2	(11)
S. cholerae suis	40	(188)	S. poona	2	(12)
S. oranienburg	15	(274)	S. wichita	2	(4)
S. newport	14	(340)	S. thompson	1	(24)
S. enteritidis	5	(70)	S. daytona	1	(1)
S. bareilly	4	(65)	S muenchen	1	(22)
S. montevideo	3	(198)	S. bovis morbificans	1	(14)
S. panama	3	(113)	S. eastbourne	1	(5)
S. anatum	3	(121)	S. javiana	1	(1)
S. paratyphi B	2	(143)	S. newington	1	(46)
S. derby	2	(99)	S. havana	1	(2)
S. paratyphi C	2	(5)	S. worthington	1	(2)
S. manhattan	2	(30)	S. arizona*	1	(1)
			Total	174	

*S. arizona has recently been eliminated from the Kauffman-White Schema and has been inserted in the "arizona group" of the paracolon bacilli.

types are too small to justify a statistical evaluation, 4 of the types, SS. *typhi murium*, *cholerae suis*, *oranienburg*, and *newport*, lend themselves to an appraisal (Table 2). In our material SS. *typhi murium*, *oranienburg* and *newport*, display a case fatality of between 4.1 and 5.5%. The average case fatality of 22 other types was 3.2% and that of all Salmonellae 5.3%. In contrast to these is S. *cholerae suis* with 21.3%. This figure is in agreement with the observations of other workers in this field, particularly with those of Edwards, Bruner and Moran[2] who reported 24 fatalities among 149 S. *cholerae suis* infections (16.1%), and our own previous calculations. Most of the cholerae suis cultures were isolated from blood, pus, other parenteral sources, and from post mortem material. Isolations of cholerae suis from feces and from healthy carriers were relatively rare. Among our entire material we encountered only 3 healthy carriers, while Edwards Bruner and Moran have not observed a single healthy human carrier of S. *cholerae suis*. In the fatal cases isolations from feces were outnumbered by those from the blood stream and other local manifestations. Seventy-four positive blood cultures and 16 spinal cultures were recorded. Pus and exudates yielded 18 Salmonellae; 5 urines were found positive, and 21 organs proved to be infected at autopsy.

TABLE 2.—CULTURES ISOLATED FROM FATAL CASES IN RELATION TO TOTAL NUMBER.

Type	*No. of Cultures*	*Fatal*	*Per cent*
S. typhi murium	1155	63	5.2
S. cholerae suis	188	40	21.3
S. oranienburg	274	15	5.5
S. newport	340	14	4.1
22 other types	1322	42	3.2
Total	3279	174	5.3

The *age distribution* of 156 fatalities is significant. Thirty-four infants of less than 1 year died principally of meningitis and severe diarrhea. In the age groups between 1 and 10 years there were only 10, between 10 and 50 years 42 fatalities. Beyond the age of 50 the mortality rate rises sharply. There were 70 deaths in this group. Computed on all cultures from the respective age groups, the case fatality amounts to 15% in the group over 50 years, 5.8% in

the infant group, and about 2% between 1 and 50 years. In patients beyond 50 approximately two-thirds of the deaths are to be attributed exclusively to the Salmonella infection. In about one-third a fatal Salmonella invasion occurred as a complication to an unrelated disease, arteriosclerosis, hypertension, pneumonia, heart disease, diabetes, cancer and others. It appears that the resistance of such debilitated, elderly individuals becomes so weakened that a Salmonella carried for an indefinite time in the intestinal tract invades the blood stream. This may constitute the "last straw" in a precarious or sinking condition.

A few instances may illustrate this point: 1, A 74 year old man fractures his femur, develops a fatal pneumonia with S. *cholerae suis* in his blood stream. 2, A 54 year old diabetic woman dies of a neck carbuncle from which S. *typhi murium* was isolated. 3, A 70 year old man with a chronic lymphatic leukemia dies of a lung abscess caused by S. *cholerae suis*. 4, A 69 year old man dies in coma after a bout of high fever and an S. *enteritidis* septicemia; at necropsy, diabetes, bronchopneumonia, arteriosclerosis, septicemia. 5, From the blood of a 68 year old woman with high fever, S. *typhi murium* was isolated. Her necropsy revealed a carcinoma of the lung. 6, A 70 year old man develops an S. *cholerae suis* septicemia with very high fever. On the 8th day he dies suddenly. The autopsy reveals a dissecting aneurysm of the descending aorta. These few selected examples demonstrate Salmonellae complicating severe underlying disease and accelerating the downward trend.

Table 3 shows the most frequently recorded clinical diagnoses in fatal cases, and the principal types involved. These are acute gastroenteritis with fever, vomiting and diarrhea, involvement of lungs and pleura, meningitis, septicemia without further qualification, typhoidal syndromes not caused by S. *typhosa*, bacterial endocarditis, diseases of the gallbladder, appendicitis and peritonitis. Rarer diagnoses such as abscesses, carcinoma, ruptured aneurysm, pyelonephritis, osteomyelitis, heart disease, uremia, are omitted in the Table. These diagnoses have been taken from questionnaires returned by the source laboratories or the attending physician. Most of the pertinent information was complete and gave a clear picture of the Salmonella infection and its correlation with the fatal clinical course. Acute gastroenteritis, meningitis, bacterial endocarditis, peritonitis, cholangitis, appendicitis, with focal Salmonella findings in exudates, spinal fluid, blood and heart valves, belong to this category. In other instances, the information was incomplete and less conclusive concerning the causal connection of Salmonella infection and

TABLE 3. FREQUENTLY RECORDED DIAGNOSES IN FATAL CASES, AND TYPES INVOLVED.

Diagnosis	*No. of Cases*	*S. typhi murium*	*S. cholerae suis*	*S. newport*	*S. oranienburg*	*22 Other Types*
Meningitis	18	4	2	1	1	10
Fever, vomiting, diarrhea	63	28	7	8	9	11
Pneumonia, Pleurisy	20	5	7	3	2	3
"Septicemia"	18	5	6	2	3	2
Typhoidal Syndrome	8	1	4	–	–	3
Bact. endocarditis	10	3	6	–	–	1
Appendicitis, Peritonitis, Cholecystitis	14	4	3	–	4	3

the fatal outcome, as in the unqualified diagnoses—septicemia, pyelonephritis, uremia, and so on. Finally in a few case histories, the causal correlation of Salmonella and death is doubtful. Salmonella invasion may have occurred under agonal conditions, in other cases the finding of Salmonellae may have been altogether incidental, considering that the incidence of healthy carriers among the general population is not negligible. On the other hand there seems little doubt that the few cases in which Salmonella have been incorrectly accused are greatly outbalanced by those instances of severe Salmonella infections in which a subsequent death has not been reported because it had occurred after the questionnaire had been completed.

Summary. 1. One hundred and seventy-four fatalities among 3279 patients infected with Salmonella were evaluated. Typhoid patients, military personnel, and individuals without an adequate diagnosis were excluded.

2. Altogether, 26 Salmonella types were involved. Among these, 4 types: SS. *typhi murium, cholerae suis, oranienburg*, and *newport* accounted for three-quarters of all fatalities. The average fatality rate of Salmonellae was 5.3%, while S. *cholerae suis* stands out with 21.3%.

3. Patients above 50 had the highest fatality rate, followed by infants under 1 year of age. The incidence of Salmonella deaths in the age groups between 1 and 50 was low. A considerable number of the patients above 50 were suffering from severe, not directly related diseases.

4. While among the fatalities acute gastroenteritis was frequent, particularly among infants, many parenteral manifestations occurred; such as meningitis, involvement of lung and pleura, bacterial endocarditis, septicemia, peritonitis, cholecystitis, pyelonephritis, osteomyelitis, and abscesses. Not in all fatal cases, particularly in older patients, was Salmonella the exclusive cause of death.

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BLOOD PYRUVATE LEVELS FOLLOWING INTRAVENOUS GLUCOSE INJECTIONS IN AGED MALES*

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In a previous study[15], it was found that the time required for the blood glucose level to return to normal following the intravenous administration of glucose was significantly longer in aged subjects than in young adults. Whether this decreased glucose tolerance is evidence of an insulin deficiency is not known but deserves further study. The purpose of the present study was to determine the relation of blood pyruvate level to the age change in response to glucose injection.

In 1941, Bueding, Stein, and Wortis[3] found that the blood pyruvate level following glucose ingestion in normal adults rose to a peak at 1 to 2 hours and subsequently fell to fasting levels within 3 to 4 hours. In patients with thiamine deficiency, the rise in the blood pyruvate levels was slower, higher, and more prolonged. The changes in normal subjects have been confirmed by Gillman and Goldberg[8]. After glucose is administered intravenously the same type of response is found, except that the peak of the blood pyruvate level is reached at 40 to 60 minutes[2].

In depancreatized dogs there is no rise in the pyruvate level of the blood after glucose injection unless insulin is administered or the blood glucose level is kept at 750-900 mg. per 100 cc. for 3 to 5 hours[1]. Patients with diabetes mellitus also show little or no rise in blood pyruvate after glucose consumption unless they are given insulin[5,9,13]. Hence it is generally thought that insulin is necessary to obtain a rise in the blood pyruvate level after glucose ingestion or injection.

Since insulin effects the rise in the blood pyruvate level after glucose injection, it was thought that a study of the blood pyruvate levels after glucose injection in elderly subjects might give some indication as to whether the prolonged† glucose tolerance curves in these subjects is due to an insulin deficiency. The present paper reports the results of a study of the pyruvate levels in blood after the injection of glucose in patients with diabetes mellitus, elderly subjects with prolonged intravenous glucose tolerance curves, and elderly subjects with normal intravenous tolerance curves.

Experimental Methods. *Subjects.* The diabetic subjects were selected from the Home for the Aged and the Chronic Hospital of the Baltimore City Hospitals. Their diabetes was of at least 5 years duration and all patients were receiving protamine zinc insulin while some were receiving regular insulin in addition. When insulin was omitted prior to the test they all manifested a fasting hypergly-

* The technical assistance of Diana Guarino, Janis Parsons, and Patricia Skinner is gratefully acknowledged.

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† Throughout this paper the phrase, "prolonged glucose tolerance," refers to a glucose curve which does not return to the fasting level ± 2 mg. per 100 cc. in 120 minutes or less after the intravenous injection of 50% glucose in distilled water[11].

cemia and glycosuria and 5 of the 7 had ketonuria as well.

The remainder of the subjects were selected by history and physical examination from the same source. No one was included in the series who gave a history of peripheral neuritis, glycosuria, chronic alcoholism or any type of liver disease. All subjects were free from fever, hepatomegaly, cardiac decompensation, glycosuria or evidence of nutritional deficiency.

All subjects were ambulatory and on a basic diet of protein, 86.5 gm. per day; fat, 103 gm. per day; and carbohydrate, 286 gm. per day with a total caloric intake daily of 2413 for at least 2 weeks prior to the test. In addition, the subjects received thiamine hydrochloride, 50 mg. per day intramuscularly for the 3 days preceding the test. All of the subjects were between 50 and 84 years of age with the exception of 2 who were 44 and 45 years old respectively. Thirty subjects were tested, 7 patients with diabetes mellitus, 13 with normal intravenous glucose tolerance tests, and 10 with prolonged intravenous glucose tolerance tests.

METHODS. The experiments were performed with the subjects under basal conditions. The diabetic patients had not received insulin for 72 hours preceding the test. A No. 19 Quincke stylet needle was inserted into the left or right femoral artery and 2 fasting blood specimens were drawn. Fifty cc. of 50% glucose in distilled water were then injected into the right or left basilic vein during a period of 2 minutes. Blood samples of 5 cc. were drawn at 5 and 10 minutes after the beginning of the injection and every 10 minutes thereafter for 2 hours.

The blood samples were placed immediately in tubes containing 100 mg. potassium oxalate, 50 mg. sodium fluoride, and 25 mg. iodoacetic acid. Three cc. of the blood of specimens drawn at 0, 10, 30, 50, 70, 90, and 110 minutes were pipetted immediately into 12 cc. of trichloroacetic acid for the preparation of the filtrates for the pyruvate analyses. The remainder of the blood was left in the tubes until the completion of the experiment when the glucose analyses were done on every blood specimen obtained.

Pyruvate was determined by the Bueding and Wortis modification of Lu's method[4]. In this laboratory the range of duplicate analyses on multiple filtrates ($N = 9$) from 1 blood sample was 0.08 mg. per 100 cc. The range of recovery of pyruvate added to plasma sample was $\pm$ 10% in 15 experiments. The blood filtrates from the diabetic patients were treated according to Klein[10] for the removal of interfering substances. The glucose analyses were done by the method of Nelson[12]. The color developed in both procedures was read on a Coleman Model 14 Spectrophotometer at 520 mμ.

TREATMENT OF DATA. Individual tolerance curves were drawn for each test. From these curves the time to return to the fasting level $\pm$ 2 mg. per 100 cc. was estimated. All subjects whose blood glucose level returned to the fasting value within 120 minutes or less were regarded as normal; all others as abnormal. For each of the 3 subject groups, the means and standard deviation of age and time for glucose concentration to return to fasting levels were calculated. The mean and standard deviation of the pyruvate levels, and of the change of each point on the pyruvate curve relative to the fasting level were also calculated. Using the "t" test of Fisher[7] differences between comparable means of the various subject groups were evaluated for statistical significance.

Results. GLUCOSE TOLERANCE CURVES. *Age.* There was no significant difference between the mean ages of the diabetic, normal, and abnormal tolerance groups. The mean ages were 68.3 years for the diabetic group, 61.0 years for the group with normal glucose tolerance tests, and 67.4 years for the subjects with a decreased tolerance to glucose. The range of age for these groups were 57 to 83 years, 45 to 84 years, and 44 to 83 years respectively.

Time to Return to Fasting Levels. In the subjects with normal glucose tolerance curves, the time in minutes for the blood glucose level to return to the fasting value ranged from 60 to 120 minutes with a mean value of 92.0. In the group with abnormal glucose tolerance tests the range was 130 to 180 minutes with a mean value of 143.9.

In the diabetic group, the majority of the glucose tolerance curves were still so elevated at the end of 2 hours that a graphic estimation of the time to return to the fasting level could not be made.

Blood Pyruvate Levels. There were no significant differences between the fasting levels of the 3 groups. The

mean fasting blood levels of pyruvate for the groups were 1.28 mg. per 100 cc. for the elderly subjects with normal glucose tolerance curve; 1.44 mg. for the subjects with prolonged glucose tolerance curves; and 1.50 mg. for the diabetic group.

Following the injection of glucose, the blood pyruvate levels in the non-diabetic groups rose, reaching a maximum of 1.76 and 1.91 mg. per 100 cc. at 30 to 50 minutes after the beginning of the injection. In all subjects except 1, the pyruvate level had returned to the fasting level or below at the end of 2 hours. In the patients with diabetes mellitus, the blood pyruvate levels did not change with the exception of 2 patients whose pyruvate levels rose to a peak at 50 and 70 minutes respectively. In both cases the pyruvate level had not returned to fasting level at the end of 1 hour and 50 minutes. There was no significant difference between the peaks of these curves. The mean curves of the 3 groups are presented in Fig. 1.

Changes in Pyruvate Level. In Fig. 2 are presented the mean changes of blood pyruvate levels in mg. % from the fasting levels in the 3 groups. The difference between the mean values at 30 minutes of the diabetic group and the group with normal glucose tolerance tests is significant beyond the 1% level ($t = 3.13$ $N = 17$), whereas the difference between the diabetic group and the group with abnormal glucose tolerance tests is significant at the 2 to 3% level ($t = 2.57$ $N = 15$). There was no significant dif-

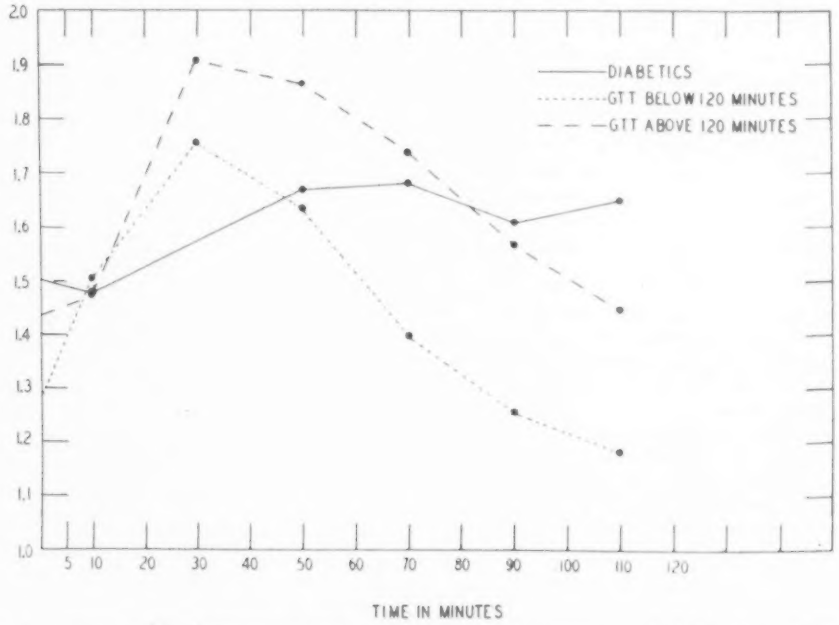

FIG. 1. Average blood pyruvate levels following the intravenous administration of 50 gm. glucose. Glucose administered at 0 time.
——— Average values for 7 patients with diabetes mellitus.
- - - - - Average values for 13 aged patients requiring less than 120 minutes for recovery of blood glucose level.
— — — Average values for 10 aged patients requiring more than 120 minutes for recovery of blood glucose level.

ference between the maximum mean change of the 2 non-diabetic groups.

The subjects with normal glucose tolerance tests had a maximum mean change of 0.48 mg. per 100 cc., and the subjects with abnormal glucose tolerance tests a maximum mean change of 0.42 mg. Both of these maxima occurred at 30 minutes after glucose injection. The diabetic group showed a maximum mean change of 0.18 mg. at 70 minutes after glucose injection.

Discussion. The maximum mean change of 0.48 mg. per 100 cc. in this study is in close agreement with the maximum mean change of 0.44 mg. obtained by Bueding, Stein, and Wortis[3] after the oral administration of glucose, but is lower than the maximum change of 0.64 mg. which Bueding and Goldfarb[2] reported after the intravenous administration of glucose. The latter authors, however, gave a much larger dose of glucose than was administered in this study.

The 2 diabetic patients who showed a rise in their pyruvate level were both very mild diabetics whose usual daily dosages were 10 and 15 units of protamine zinc insulin respectively. These rises are reflected in the mean curve for the diabetic group (Fig. 2) at the 50 and 70 minute points. Slight rises were also reported by Root, Stotz, and Carpenter[13] in 2 very mild diabetics not receiving insulin and with diabetes mellitus of short duration.

Since the mean fasting pyruvate

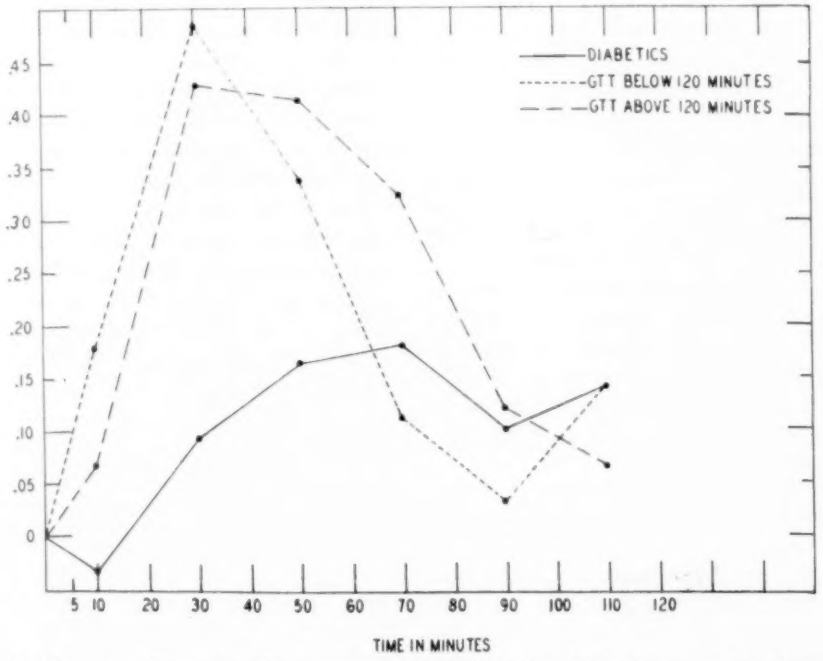

FIG. 2. Average change in blood pyruvate level following the intravenous administration of 50 gm. glucose.

———— Average values for 7 patients with diabetes mellitus.

- - - - - - - Average values for 13 aged patients requiring less than 120 minutes for recovery of blood glucose level.

— — — — Average values for 10 aged patients requiring more than 120 minutes for recovery of blood glucose level.

value of the diabetic group is considerably higher than the mean fasting value of the other 2 groups and since the increase above fasting is much less in the diabetic group, the mean values of the 3 groups are close together at the 30 minute specimens (Fig. 1). However, when the changes from fasting level are compared in the 3 groups (Fig. 2), the difference in response of the various groups becomes evident.

The fasting pyruvate levels in some cases were higher than the normal of 1.30 mg. per 100 cc. set by Bueding *et al.*[6]. This is due to the fact that arterial blood was used, since it has been shown that the pyruvate concentrations in peripheral arterial blood is often higher than in venous blood[14]. Also in 1 patient in whom A-V pyruvate levels were followed during a typical experiment, the arterial pyruvate level was always higher than the venous level of pyruvate, the mean A-V pyruvate difference being + 0.28 mg. The absence of the typical response of a high and prolonged pyruvate level usually associated with avitaminosis makes it unlikely that the high fasting values were due to this cause.

Since the blood pyruvate increase of both non-diabetic groups was similar and since both differed significantly from the diabetic group, it is thought that the decreased glucose tolerance of the aged is not due to an insulin deficiency.

The possibility exists, however, that a normal pyruvate response is obtained with a minimal insulin deficiency. In favor of this hypothesis is the fact that the 2 patients with diabetes mellitus in this study who had a rise in pyruvate required only 5 and 10 units of protamine zinc insulin respectively. Furthermore, 2 mildly diabetic patients not requiring insulin, reported by Root, Stotz, and Carpenter[13], showed a rise in pyruvate after glucose injection. However, not all mild diabetics show a rise in pyruvate after glucose since 2 such patients in the latter series who required no insulin had no rise in their pyruvate level.

Because some of the diabetic patients with little or no insulin requirements had no rise in pyruvate level after glucose, whereas all the non-diabetic subjects with prolonged glucose curves had a normal response, these prolonged curves could not be due entirely to minimal insulin deficiency.

Summary. A study of arterial blood pyruvate levels after the intravenous injection of 50 cc. of 50% glucose in distilled water was made in 3 groups of elderly subjects: 1, a group with normal glucose tolerance curves; 2, a group with prolonged glucose tolerance curves; and 3, a group of diabetics who had been without insulin for 72 hours.

The blood pyruvate levels in the 2 non-diabetic groups increased from resting values of 1.29 and 1.42 mg. per 100 cc. to 1.72 and 1.91 mg., respectively, at 30 to 50 minutes after the glucose administration. In patients with diabetes mellitus, the rise was not significant (1.50 to 1.62 mg. per 100 cc.). The differences between the rise observed in the 2 non-diabetics and diabetic groups was statistically significant. These results indicate that insulin deficiency is not the primary factor responsible for the prolonged glucose tolerance curves observed in aged subjects.

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THE SUBSTRATUM OF CENTRAL NERVOUS SYSTEM MANIFESTATIONS IN SYPHILIS*

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It is usually assumed that neurologic or psychiatric symptoms present in a patient with positive serologic reactions are of syphilitic etiology. Necropsy, however, frequently reveals the presence of pathologic conditions other than syphilis which can account for the symptoms, so the question arises as to the relative importance of the multiple etiologic factors. It seemed worthwhile, therefore, to review the autopsies studied in the laboratory of neuropathology of the Philadelphia General Hospital and to analyze the cases which presented either serologic or pathologic evidence of syphilis.

The study covers 8 years, 1935 to 1940 inclusive, 1946 and 1947. The intervening years were likewise investigated, but omitted because during the war the records were incomplete. In the 8 year period there were 3104 neuropathologic studies in a group of 14,311 general necropsies. From the group of neuropathologic autopsies, 346 presented either serologic or postmortem evidence of syphilis. This study is based on 339 cases, as in 7 cases clinical data were inadequate. It is noteworthy that the number of cases drawn from each calendar year shows a homogeneous selection indicating little change in the incidence of syphilis accompanied by nervous or mental symptoms between 1935 and 1947. In view of the statistical studies to follow, it should be stated at this time that there are no significant differences in sex and color in the neuropathologic cases at this hospital.

The cases were divided into 3 groups on the basis of the pathologic changes found. The first group of 105 includes those in which a diagnosis of central nervous system syphilis was established by histopathologic study. Paresis or taboparesis was present in 75, meningeal or vascular syphilis in 21, spinal syphilis in 9 (comprised of tabes dorsalis 5 and hypertrophic pachymeningitis 4). Criteria for diagnoses are as follows: Paresis: alteration of the cortical architecture due to cell loss and microglial and astrocytic proliferation associated with perivascular and subarachnoid infiltration by chronic inflammatory elements; meningeal syphilis: inflammatory reaction of lymphocytes

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and plasma cells limited to the subarachnoid and perivascular spaces; vascular syphilis: intimal proliferation without degeneration with or without lymphocytic infiltration of the vessel coats. Criteria for the diagnoses of tabes dorsalis and hypertrophic pachymeningitis are too well established to require definition. The statistical findings of this group reveal a mean age of 44.6 ± 3.0 years at death. Ninety-nine % confidence limits are used as a statistical method throughout this paper[1]. There are no significant race or sex differences in this group.

The second group includes 126 cases with nervous or mental symptoms associated with luetic cardiovascular disease but without histologic evidence of central nervous system syphilis. The mean age of this group is 48.7 ± 2.8 years. In contrast to the first group, there are highly significant preponderances of males over females, 2.1 to 1, and of colored over whites, 2.5 to 1.

The third group contains 108 cases with neurologic signs and symptoms in which the only evidence of syphilis was positive serological tests. The mean age of this group is 48.6 ± 3.5 years. There is no sex difference, but the colored outnumber the whites in a ratio of 2.9 to 1.

Statistical comparison of the 3 divisions shows a pronounced difference between the mean ages of the first with central nervous system syphilis and either or both of the other 2 without luetic involvement of the nervous system. In other words, patients with central nervous system syphilis died younger than other luetics. In the first category the incidence of central nervous system syphilis in the colored is no greater than in the white, whereas in the other 2 groups there are great differences in the color ratio, the colored predominating over the white.

Further analysis from a clinicopathologic standpoint shows that in the first group, the syphilitic involvement of the central nervous system was primarily responsible for the neurological signs and symptoms in 76 of the 105 cases (72%). In the other 29, however, in addition to histologic evidence of cerebral syphilis, there were complicating non-specific diseases potentially capable of causing the clinical picture either in part or in its entirety. These included:

Metabolic intoxications (chronic alcoholism, hepatic insufficiency and diabetic acidosis)	9
Non-luetic heart disease with decompensation	7
Infections (pulmonary and genitourinary abscesses)	4
Head trauma	4
Cerebral atheroma	3
Chronic plumbism	1
Sickle cell anemia	1

Seventeen of these 29 had general paresis and 12 meningeal and, or, vascular syphilis. It should be stressed that of the 105 cases in this group 38 (36%) presented post-mortem evidence of luetic cardiovascular disease. Statistically this is of more than casual occurrence, 99% confidence limits being 25 to 49%.

In the second group the central nervous system signs and symptoms were attributable to luetic and cardiovascular disease in 71 of the 126 cases (56%). In 49 of the 71 (69%) neurologic manifestations were the result of acute and extensive cerebral vascular accidents. Twenty-two were admitted to the hospital primarily for cardiovascular disease accompanied by coma, convulsions, psychic disturbances, headache or blurred vision. Forty-one of these cases (58%) died within a week after admission, and 54 (76%) within 2 weeks. In 46 (65%) the onset of the central nervous system symptoms were associated with signs of cardiac decompensation. It should be noted here that

while luetic heart disease was present in all patients, it was associated in 40 cases (56%) with other types of cardiac disease.

In 55 cases the luetic cardiovascular disease was limited to asymptomatic aortitis and was unrelated etiologically to the production of nervous or mental symptoms. These cases have been included in the third group.

The third group, therefore, is increased to 163 in which the etiology of the signs and symptoms of nervous or mental disorder cannot be attributed to syphilis. In 48 cases (30%) the symptoms were of short duration and were manifest by coma, convulsions, psychic disturbances, headache and blurred vision. This group contained metabolic diseases, 23; infections, 15; and non-specific cardiovascular disease, 10. In 41 (25%) there occurred cerebral vascular accidents, 31 of which were associated with non-luetic cardiovascular disease, and 10 occurred during the terminal phase of wasting illnesses and surgical shock. In 74 cases (45%) the signs and symptoms were due to intracranial disease unrelated to syphilis; 30 of these had non-luetic infections of the brain and meninges, 16 head trauma, 15 intracranial neoplasms, 7 malformations of the central nervous system (including aneurysms), and 6 had chronic degenerative disease.

Comment and Summary. In a group of 339 cases with serologic or pathologic evidence of syphilis, indisputable histopathologic evidence of central nervous system involvement was present in only 105 (31%). In 29 of these, however, the accompanying non-specific changes must be considered as an equipotential etiologic factor. In an additional 71 cases, central nervous system symptoms might be accounted for on the basis of existent luetic cardiovascular disease in spite of the absence of luetic involvement of the nervous system. Syphilis, therefore, may be incriminated as a possible factor in 176 cases (52%). In the remaining 163, pathologic study suggested non-specific disease as the predominant cause, and syphilis was incidental rather than primary in respect to the nervous and mental symptoms.

Extreme caution, therefore, must be exercised regarding neurologic manifestations in a patient with positive serology as due to syphilis alone. The possibility that non-luetic pathology may be equally or entirely responsible always must be borne in mind. From the viewpoint of practical clinical management positive serologic reactions should not justify the abandonment of further diagnostic studies which may more positively delineate other causes. From the therapeutic aspect adequate anti-luetic treatment should be mandatory. It must be recognized that therapeutic failure may result from lack of critical evaluation of non-luetic etiologic factors. Supplemental treatment, directed toward the non-specific disease, is also indicated even in the presence of central nervous system syphilis.

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ABDOMINAL EPILEPSY*

A Clinical Entity

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Epilepsy, in its protean forms, is the end-symptom display of "irritated" discharging neurons, the clinical features of which are fashioned by the site of the primary focus of discharge, and by spread of excitation by contiguity to adjacent fields, and by projection to distant gray matter. Thus an uncinate fit may retain its integrity as an epileptic entity if the discharging gray matter stays within bounds, but once the electrical potentials spill over and the spread of excitation reaches other areas eventuating in a dreamy state or a major epileptic fit, the olfactory symptom is termed an aura or mere precursor to the main event. To the initiated, however, the isolated olfactory manifestation, when adhering to the phenomenological pattern of epilepsy, is readily recognized as a cortical dysrhythmic disorder or the attack itself. Other atypical fits or epileptic variants[8a-k], such as paroxysmal transient headaches, fits of unreasonable anger or assaultive behavior, bouts of pathological laughter, syncopal attacks (encephalo-syncope), vasomotor Jacksonian epilepsy, seeing one's own image as an epileptic equivalent, perseveration of visual images, fits of micropsia and macropsia, recurrent nausea and vomiting, choking sensations, laryngeal epilepsy, paroxysmal abdominal pain (abdominal epilepsy) and other variants expressed in the motor, sensory and autonomic spheres, which occur more frequently than orthodox epileptic seizures, too often are unrecognized, or have not been given the official status of an epileptic disorder because hitherto the boundaries of the epileptoid states have not been clearly mapped. Among this array of epileptic variants, abdominal epilepsy appears more commonly than is appreciated. Paroxysmal abdominal pain usually is misdiagnosed in children, as "navel colic", mesenteric adenitis, hypoglycemia, behavior disorder, and sundry other things. In adults the diagnoses have encompassed most of the disorders of the gastro-intestinal tract, and genito-urinary system, many of the affections of the thoracic viscera, vertebra, spinal cord and peripheral nerves, and the final note frequently ending with the despairing stigma of psychoneurosis. Much too often these patients are operated upon once or several times and an innocent appendix or other organ is removed, or the surgeon retreats empty handed.

Convincing experimental and clinical data have been presented, concerning the effects of lesions or stimulation of cortical areas 6, 5, and 3 of Brodmann, and of the diencephalon upon gastro-intestinal activity, mainly through the work of Fulton and his co-workers[4a-e], Spiegel, Weston and Oppenheimer[14], Penfield *et al.*[11a,b], and Cushing[1]. Recently Davey and Kaada[2] working in Fulton's laboratory, have confirmed the

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results obtained by Fulton and Watts[4a-c] in observing increased gastro-intestinal movements by stimulation of area 6. They noted a similar result upon stimulation of part of area 8 in the monkey, and in addition, found increased secretion of gastric juice with high pepsin concentration. Penfield[12] has intimated that stimulation of parts of the operculum may affect gastro-intestinal activity. There appears to be an extensive autonomic band reaching from the tip of the temporal lobe to the cingular gyrus, and it seems that the anterior insula, uncus and other basal parts of the forebrain may influence gastro-intestinal motility[6].

The elaborate work of LeGros Clark[7] has established the relationships existing between various areas in the frontal cortex and the hypothalamus and thalamus in a 2-way transmission of impulses. By the method of physiological neuronography, Ward and McCulloch[15] have demonstrated frontal projections on the hypothalamus, and with our present attention focused partly on one of these areas, area 6, their observation that strychninization of area 6a fired the lateral hypothalamic area, the mamillary nucleus and the posterior hypothalamic area, is of interest. Therefore it will be seen that gastro-intestinal function is served or influenced by many cortical areas, and the diencephalon, either directly or indirectly, through projection fibers.

Fitch, Pigott and Weingrow[3], in an extensively documented analysis of the gastro-intestinal phenomena observed in epileptics, stressed the significance of certain spheres of cortico-diencephalic influence upon the motor, sensory and secretory functions. Their studies dealt with known epileptics who manifested gastro-intestinal disturbances, and hence the problem of diagnosis was not at issue.

By contrast I wish to suggest the *a priori* consideration of paroxysmal abdominal pain and perhaps other gastro-intestinal syndromes as a distinct form of epileptic variant, capable of primary diagnosis in cases wherein overt epileptic displays such as convulsive seizures or loss of consciousness are absent or appear at rare intervals.

In previous reports[9a-e] I have cited cases of abdominal epilepsy which had escaped recognition as such, and outlined the clinical characteristics, method of study, diagnosis and treatment. Since then other reports[13a-h] have begun to appear of similar and related cases in which the diagnosis of abdominal epilepsy was established, usually after the patient had been previously studied exhaustively and unrewarding abdominal operations had been performed.

Since abdominal pain is one of the commonest symptoms the physician is called upon to interpret, how can he recognize it as that of abdominal epilepsy without resorting immediately to extensive studies which test the patient's physical and financial resources?

The syndrome should conform in behavior to the multiform "seizure pattern" of epilepsy defined by Wilson[16] as "any fugitive, paroxysmal disorderly, uncontrolled and recurrent manifestation of any neural process might be regarded as a fit, and this on any level of the neuraxis . . . as for fits implicating visceral centers, there may be no interference with the conscious stream, no involvement of skeletal muscles and, in fact, none of the usual signs of epilepsy, so that divergence of the formula may be extreme . . . The least mutable of accepted fit characters comprise sudden onset, brief duration and recurring habit; yet some forms are protracted (notably epilepsia partialis continua), repetitions may be extraordinarily infrequent, and brevity loses significance when the aura (as in some uncinate cases) is drawn out."

The abdominal pain is paroxysmal and may constitute the sole or domi-

nating feature of the syndrome, or it may be the significant center about which cluster one or more of such symptoms as "peculiar feelings", nausea, occasionally vomiting, rarely diarrhea, pallor, sweating, "rumbling sounds" in the abdomen, periodic attacks of abrupt behavior disturbances, nightmares, clonic movements of the abdominal muscles and rarely of the limbs, without loss of consciousness, and post-ictal "achiness", exhaustion, and sleep. This latter group can be recognized as consisting of pre-convulsive and post-convulsive epileptic phenomena or abortive fits in full right, and should therefore act as a guide to or corroboration of the epileptic nature of the abdominal pain.

The provocative causes of abdominal epilepsy are those of any form of epileptic display. The abdominal pain may represent a symptomatic expression of an organic lesion, of any nature, impinging upon and irritating the ganglion cells of the areas of the brain previously discussed as mediating gastro-intestinal activity. Among 18 cases I have studied, approximately 50% were of organic origin, due mainly to cerebral trauma but including brain tumor, tuberous sclerosis, and scarlatinal encephalopathy. Of Stevens'[13d] 12 cases, ½ had evidence of organic disease of the brain. Schapiro's case[13c] had several head injuries. Those individuals without a history or neurological evidence of organic disease, for want of a better classification, fall into the so-called idiopathic, cryptogenic or genetic category, and the acknowledged precipitating factors of ordinary epilepsy prevail here as well. Of the patients studied electroencephalographically, among the authors cited and in my series, 67 to 80% had abnormal electrograms.

The approach to the study of these patients rests largely upon history, electrographic abnormalities and the response to the therapeutic test with anticonvulsants. Almost invariably very extensive studies of the various systems, especially the gastro-intestinal tract, already have been done, disclosing normal findings before the consideration of abdominal epilepsy is entertained. A thorough going history in all phases is the first essential, and it should be one in which the threads of the pattern of epilepsy are sifted out and woven together. Neurological and frequently Roentgen-ray examination of the skull already have been done; if not, they should be, and in addition when indicated cerebrospinal fluid studies, cerebral angiography, cerebral air studies, and mandatory electroencephalography. With respect to the latter, a normal electrogram should not influence the diagnosis negatively if the history and therapeutic test validate it. The final step in study has recourse to the empirical method of the therapeutic test in which the response of the syndrome of abdominal epilepsy to an anticonvulsant regimen should be one of either a complete control of symptoms or radically altering them, return of symptoms upon cessation of treatment, and abeyance of symptoms when treatment is reinstituted. Abnormal electrograms should be favorably modified by anticonvulsant medication, as has been shown by Goldman[5].

Treatment, in brief, is dependent upon the data gathered in the study[10]. Organic lesions of the brain amenable to surgery are so treated; constitutional, infectious, metabolic and other disorders which have a causal relationship to the paroxysmal abdominal pain should receive treatment specifically directed. The symptomatic treatment consists of the broad aspect of the total attack of any epileptic problem, namely guidance of the social, physical and emotional life of the patient, a properly designed dietary regimen and appropriate medication. The latter consists

of the flexible use either singly or, more effectively, in combination of the following drugs: 1, dilantin sodium (diphenylhydantoin sodium); 2, mesantoin (methyl-phenylethylhydantoin); 3, phenobarbital; and, 4, bromides (alkaline or calcium bromido-galactogluconate (Calcibronat). The results of anti-epileptic treatment in the cases, exclusive of space taking and degenerative lesions, in my series and in those cited, have been in some instances truly dramatic and on the whole almost uniformly gratifying.

Conclusion. Attention is called to the need for primary recognition of episodic attacks of abdominal pain, which fit the various criteria of a dysrhythmic disorder, as an outspoken epileptic variant, thereby providing the patient release from his symptoms and from prolonged, profitless studies and treatment.

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CHEMOTHERAPY IN VIRAL INFECTIONS* **

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CHEMOTHERAPY is not a new development in the management of some viral infections. Sulfanilamide was employed successfully in the treatment of lymphogranuloma venereum[22] and trachoma[31] as early as 1938. Inclusion conjunctivitis also was treated effectively with sulfanilamide in 1941[48]. Psittacosis was found to be favorably affected by penicillin therapy in 1947[35]. Chemotherapy remains as yet, however, far short of its potential stature in the management of viral infections. The early, and in some instances dramatic, successes which have been mentioned were not followed by similar results in other viral diseases. Among the 50 odd maladies of man which are of viral etiology only the 4 already named are surely amenable to the effects of available chemotherapeutic agents. Recent additions to the rapidly increasing list of chemical substances which possess striking therapeutic activity have not altered this state of affairs. Aureomycin[40] and chloromycetin[44] give promise of being highly effective against members of the psittacosis-lymphogranuloma group of viruses, but have shown no tendency to act against other viruses of established identity.

Trachoma, inclusion conjunctivitis, lymphogranuloma venereum and psittacosis are caused by the largest of known viruses. The members of this group appear to be closely related by serological evidence and possess antigenic constituents in common[39]. These relatively huge viruses are seen readily with an ordinary light microscope, have dimensions of the order of 250 millimicrons, and are only very slightly smaller than rickettsiae. Because of the

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** The Editor is especially happy to publish this article, as it is both an able discussion of a live subject and a memorial to an intimate friend and colleague, who was his predecessor as editor of this journal.

peculiar properties of the psittacosis-lymphogranuloma group, their large size and structural complexity, some workers have come to the view that they and the rickettsiae should be placed together in a no man's land between viruses and bacteria. This idea recently has received official sanction from the taxonomists[1]. Whatever the merits of formal classification, it does appear that this group of viruses and the rickettsiae possess some features in common as both are affected by the same chemotherapeutic substances: aureomycin and chloromycetin. For the same reason both groups of infectious agents appear to be clearly separable from that larger class of agents which may be termed true viruses.

That available antimicrobial substances, so remarkably effective in bacterial and rickettsial infections, should be without effect in all but a very few viral infections is additional evidence of the peculiar nature of viruses. The biochemical mechanisms that are affected by sulfonamides or by therapeutic substances of microbial origin and are essential for bacterial growth and multiplication appear not to be required in the process of viral synthesis. This indicates a difference in the biochemical requirements of bacteria and viruses which is undoubtedly of deep significance and may be of fundamental importance.

The history of the development of chemotherapy in bacterial infections does not show that knowledge of the metabolic requirements of microbes was of aid in discovering antimicrobial substances[7]. Indeed, in all instances their discovery was occasioned by investigations which were not concerned with particular metabolic processes. As all know, the antimicrobial effects of sulfanilamide and penicillin could not have been predicted from existing knowledge on the biochemical mechanism of bacterial growth. On the contrary, it is evident that modern chemotherapeutic substances have emerged as powerful tools which have advanced the study of bacterial metabolism and genetics. In numerous instances their use has led to increased understanding of the complex mechanism of bacterial growth.

The striking successes which attended the vigorous search for more broadly effective antibacterial agents led promptly to an intensive search for chemotherapeutic substances active in viral infections. Many thousands of substances, both of known and of uncertain nature, already have been subjected to activity tests with a wide variety of viruses. With the scanty exceptions mentioned earlier, none has yet proven of definite value in viral infections of man. There are, however, some indications that the situation may not be without hope. Fairly recent evidence from a number of laboratories suggests that with experimental viral infections of animals[29,17], plants[15], and bacteria[14] some modification of the disease process may be obtained with chemical substances. These investigations are in the earliest stages and the available data are meagre at best but enough has been uncovered to arouse interest and perhaps to stimulate further study.

Viral infections run their course and, in the great majority of instances, are followed by recovery of the host. The phenomenon of recovery is as commonly characteristic of naturally occurring viral infections of plants as it is of those of animals including man. With the exception of rabies and peach rosette there are almost no viral infections of multicellular organisms which uniformly kill the host. Some viruses appear never to cause death of the naturally infected host; potato X and mumps are instances. Of the vast num-

ber of viral infections which develop each year in human beings the number which terminate fatally is exceedingly small. So, too, with viral diseases of plants. As evidence, it may be pointed out that practically all commercially grown tomatoes are infected with tobacco mosaic virus and yet there is no dearth of this fruit.

The rule of recovery is a clear indication that in nature there exists a mechanism which serves to limit a viral infection. If the nature of this mechanism were understood clearly, could it be mimicked by artificial means and the usually favorable outcome hastened? The altered status which generally follows a viral infection is called immunity. In plants, as in animals and man, this state is characterized by insusceptibility to a second infection with the same virus. In man and animals immunity of this sort is often reflected, though not very precisely, by changes in the proteins of the serum and tissues. Such altered proteins are termed antibodies. But with plants the situation is otherwise, for no antibodies are demonstrable and yet immunity is as durable and equally as specific as among vertebrates.

Recovery begins in a few days to a few weeks after the onset of most viral infections. In general, the acute phase of the disease does not last longer than 1 to 3 weeks. In man and animals the recovery process, in most instances, is correlated fairly well with the appearance of circulating antibodies and the disappearance of the virus. That there are some striking exceptions to this rule, as for example in psittacosis[34], may be of significance. In plants the phenomenon of recovery occurs at about the same period but is unaccompanied by either the appearance of antibodies or the disappearance of the virus. Thus, it seems that recovery from viral infections is associated in zoological species with demonstrable alterations which do not occur in botanical species. In the light of these facts one is led to consider either that the mechanisms of recovery are fundamentally different in the two major divisions of biology or that similar mechanisms are involved and that circulating antibodies play little if any role in the process.

Plants, on recovery from the acute stages of viral infections, do not rid themselves of virus but usually continue to retain the agent indefinitely. In many instances the concentration of virus in the tissues of such plants is not greatly lower than that present during the primary infection. Of most significance, the virus itself is not discernibly different and possesses in unaltered degree the properties of the parent strain. Thus, the possibility that a variant or mutant virus replaces the parent during recovery seems unlikely.

As there is no recognizable alteration in the infectious agent either in plants or in animals, it appears that if we are to unravel the mechanism of recovery we must turn our attention to the host. The possibility that the tenets of classical immunology can be invoked has been examined already and the concept that the development of antibodies may be an adequate explanation for recovery has been found wanting. Other alterations in the host require consideration. Destruction of most or all cells susceptible to infection with the virus would leave the host in a situation in which further viral multiplication would be restricted or abolished and recovery could then ensue. Findings in the nasal mucosa of the ferret after infection with influenza virus[15] favor this hypothesis as, too, do the hepatic lesions in yellow fever[46]. There is, however, far more evidence against it. As examples, in poliomyelitis infected anterior horn cells may not be destroyed and may

recover normal function[2]; susceptible cells in tissue culture are not eliminated by vaccinia and other viruses and, if the medium is changed appropriately, will continue to support viral multiplication for long periods[11]; susceptible cells unquestionably remain present after recovery in plants as the virus persists in the plant indefinitely[38]; in herpes simplex the virus does not disappear and lesions caused by its activity frequently recur[41].

Alteration of metabolic systems of the host cell which are required for viral synthesis would result in changes inimical to unrestricted viral multiplication. Depletion of a single cellular metabolite essential to the energy or mass requirements of viral synthesis would be predicted to inhibit further multiplication. Similarly, changes in the rate of assimilation or utilization of such metabolites occasioned by the presence of the virus, could result in the development of an intracellular environment sufficiently different from the normal state to be unfavorable for viral synthesis. This hypothesis is supported by the well known fact that nutritional deficiencies, whether caloric or concerned only with individual nutrients, almost regularly result in increased resistance to viral infection[37]; that abnormal environmental temperatures lead to decreased susceptibility and to decreased viral synthesis as is most readily shown in poikilothermic hosts, for example the chick embryo[32]. It is further supported by the finding that a wide variety of chemical substances of dissimilar constitution leads sometimes to slight but often definite reduction in viral synthesis. Examples of restricted multiplication induced with various chemical substances are: the inhibitory effects of acridine compounds with influenza virus[24] and bacteriophage[13]; of 5-methyl tryptophane[4] and indole[9] with bacterial viruses; of analogues of purine and pyrimidine bases with vaccinia virus[47]; of tannic acid with influenza virus[23]; of polysaccharides with bacterial viruses[36], pneumonia virus of mice[29], influenza virus[25], and mumps virus[17]. That such widely different substances exert their effects through similar mechanisms appears doubtful.

Among the hypotheses which have been considered, that which relates recovery to alteration in host cell metabolism appears best to fit the available facts and provides an acceptable explanation for the marked differences between certain aspects of the recovery process in plants and animals. Moreover, if this postulate should be supported by additional work, there would be reasons to think that effective chemotherapeutic measures might be developed for viral infections.

To visualize the loci at which chemotherapeutic substances might be active in viral infections, it is necessary to have some picture of the mechanism of viral multiplications. Although there are wide gaps in knowledge, enough is known to indicate that the process can be thought of as a series of stepwise events[28], each strictly dependent upon the satisfactory completion of that preceding it. Viral synthesis goes on entirely within susceptible host cells; there is no known extracellular cycle. Indeed, during transit from one cell to another a virus is analogous to an inert particle and discloses no properties which would make it suspected of being an infectious agent. In an extracellular position viruses are in a vulnerable situation and are readily inactivated; many are highly unstable and the infectivity of some can be eliminated by normal constituents of serum[21]; the great majority are promptly neutralized by homologous antibody which, if it be present, can prevent spread from one cell to another. It is

improbable, however, that chemotherapy will succeed if the objective is merely to inactivate extracellular virus. When evidences of disease have become apparent, the viral particles which are temporarily in an extracellular position are of relatively little consequence. The problem is, what can be done about the intracellular virus which, as it undergoes multiplication, leads to abnormalities in host cell biochemistry?

If the initial essential step in the process of viral multiplication: adsorption of the virus by the cell, is prevented, no viral synthesis occurs and infection does not develop. The mechanism of the adsorption is not understood even though in some instances there is evidence pointing to the nature of the cell surface constituent which combines with the virus. With influenza virus the cell substance appears to be a mucopolysaccharide[27]; with bacterial viruses a polysaccharide[36]; with pneumonia virus of mice a protein[49]. Although adsorption by the cell is a necessary condition if subsequent steps in the process of viral multiplication are to proceed, it is not to be assumed that adsorption is regularly followed by viral synthesis. Numerous varieties of cells which are wholly incapable of supporting multiplication adsorb viruses and the surface constituents concerned with the reaction appear to be similar, if not identical, to those of susceptible cells. This has become clear in recent studies on pneumonia virus of mice[6]. Although the validity of the axiom: no adsorption no infection, cannot be doubted, the capacity of the cell to foster viral synthesis is dependent upon subtle biochemical properties which are not directly correlated with the presence of special surface constituents.

Prevention of adsorption of virus by the cell is the real basis for the success of specific prophylaxis with immune serum during the incubation period of measles, with inactivated viral vaccines which stimulate the production of antibodies against some encephalitis viruses and influenza viruses, perhaps also with active viral vaccines which induce modified infections useful against smallpox and yellow fever, although in the latter instances factors which relate to the recovery process more than to the concepts of classical immunity may be operative. But, it should be emphasized, prevention is not treatment and procedures which are highly effective in the prophylaxis of viral infections are valueless in their therapy. There is good reason for this. The evidences of viral disease derive from the altered physiology of infected cells which is an unhealthy by-product of viral synthesis. The disease process does not become manifest until well after viral multiplication is in progress. Many cells are already infected when symptoms first appear. A large proportion of the viral population is, at this period, in an intracellular position and is inaccessible to and unaffected by substances which inactivate the agent when it is outside of cells.

After adsorption of the virus by the cell, the next discernible step in the process of multiplication is penetration of the so-called cell membrane. The manner in which the virus is able to gain an intracellular position is unknown. With influenza[26] and mumps viruses the possibility has been raised that the agents may act in a manner analogous to enzymes and lead to alterations in a substance at the cell surface. But numerous other viruses appear not to act in a similar manner; an intensively studied example is pneumonia virus of mice[5]. Whatever may be the mechanism of penetration, it is followed shortly by a profound change in the cell membrane which makes it appear

to be impenetrable by certain other viruses. The best evidence for this has been obtained with bacterial viruses[8]. Except for the changes caused by viruses themselves, little progress has been made in attempts to render cells impenetrable to them by means of chemical substances. Even if this were accomplished successfully, it is doubtful that the procedure would possess any therapeutic merit. As was indicated earlier, it appears probable that the key to chemotherapy in viral infections may be disclosed by finding substances which are capable of inhibiting intracellular viral synthesis.

Following penetration of the cell membrane there occurs a step, or a series of steps, in the process of multiplication which is both fascinating and mysterious. After a latent period, the duration of which appears to be characteristic for a given virus, synthesis of new viral particles begins and goes on at what may be a fairly rapid rate. During the initial phase of the latent period no infective virus is demonstrable[14,4] and it may be that the original infecting particle is lost, or in some manner is altered in the process of setting the stage for the development of more like itself. The manner of viral synthesis has not been fully elucidated but certain of the systems which are involved have been recognized through studies with bacterial[3] and plant viruses[50,33]. All known viruses are composed chiefly of nucleoprotein and as might be anticipated present evidence points to the cellular metabolic systems concerned with the synthesis of nucleic acids and proteins as those most involved in viral synthesis.

If the rate of turnover of cellular proteins and nucleic acids must be reduced in general to affect similarly the rate of viral synthesis, it becomes highly improbable that attempts to discover effective chemotherapeutic agents, active against viral infections, will be fruitful. Substances which diminish either protein or nucleic acid synthesis within the cell would be directed against what are in all probability some of the most vital systems in cell biochemistry and could be expected to exert damaging effects on the host. If, on the other hand, more subtle aspects of the systems concerned with protein and nucleic acid synthesis are of critical significance for the process of viral multiplication, a more hopeful view of the situation may be held.

The phenomenon of viral interference raises the possibility that the critical steps may be subtle indeed and makes it unlikely that the rate of viral synthesis is merely a reflection of the over-all state of the protein and nucleic acid building mechanisms. Infection of a cell with one virus often, but not always, precludes infection of it with another. The infected cell can adsorb the second virus in normal fashion[19] but with appropriate pairs of viruses there occurs no evidence of multiplication of the second agent. Well studied instances of the interference phenomenon are to be found in the fields of plant[38], bacterial[10], and animal[12] viruses. Interference between viruses is not dependent upon serological relationship and appears to be independent of the presence of common antigenic constituents in the two agents[51]. That the phenomenon is not to be explained by classical immunological processes appears obvious from these facts, as also from the clear evidence that it is operative in plant virus infections. That cell processes which are deficient or unavailable as a result of being preëmpted during the synthesis of the first virus provide an explanation for the interference phenomenon is indicated by the findings that in very large amounts preformed but non-multiply-

ing virus can lead to a similar state[52]; that ridding a plant of virus, as upon appropriate heating[30], leads to abolition of the resistant state.

But not all pairs of viruses show interference and it is those which are capable of multiplying concurrently[19] in the same cell which command consideration relative to the present thesis. If, as has been suggested, the inability of a second virus to multiply in an infected cell is due to the unavailability of an essential metabolic process, then it appears that viruses which show interference require at least one cellular mechanism in common. Conversely, it seems logical to assume that viruses which can infect the same cell simultaneously: do not show interference, require different metabolic pathways of the host cell and, as consequence, can multiply side by side.

Both the natural recovery process and the experimental interference phenomenon are indicative that cells infected with viruses possess means which are effective in limiting or preventing viral synthesis. Simulation of either the recovery process or the interference phenomenon on injection of a chemical substance might be regarded as a step in the direction of chemotherapy in viral infections.

Not long ago attempts were made to develop a model for the study of complex infections. Complex infections are those which are induced by the combined effects of two infectious agents in concert[43]. The idea was that a viral infection might be made worse by superimposing a bacterial infection upon it. Such things are known to occur; swine influenza[42] is an example.

Pneumonia Virus of Mice (PVM). In the present instance a wholly unexpected result was obtained. The animals, which would all have died of the viral infection, recovered from it when bacteria were injected[29]. The virus employed is an agent termed pneumonia virus of mice (PVM), and the bacterium used is a non-hemolytic streptococcus designated MG. This surprising outcome was readily reproducible and could be obtained equally well with a number of other bacterial species. But a similar issue did not result when another virus, in this case influenza, was employed.

This bizarre finding seemed of sufficient interest to warrant detailed investigation and a variety of experiments were carried out which had as their primary objective determination of the nature of the bacterial component responsible for the apparent therapeutic effect. It was a relatively simple matter to show that the substance is present in cell free extracts of streptococcus MG, as well as in similar extracts of a number of other bacterial species; that it is non-dialysable, precipitable with alcohol and unaffected by heating at 100°C. These findings indicated that the substance is of large molecular size and remarkably stable, which raised the possibility that it might be a polysaccharide. Experiments with various enzymes, precipitants and numerous other chemical reagents lent support to this idea and the nature of the bacterial component appeared established when it was found that purified polysaccharides derived from certain bacterial species gave closely similar results[29].

Indications that the structural configuration of the polysaccharide molecule might play a decisive role appeared early. Whereas capsular polysaccharides derived from streptococcus MG and from Friedländer bacilli, types A, B, and C, are highly active, those derived from pneumococci, Types 1, 2, and from *S. salivarius* possess no activity[29,17]. When it is recalled that the polysaccharide of Friedländer bacillus Type B and that of pneumococcus type 2 give cross serological

reactions and therefore possess antigenic groups in common, the difference in their activity relative to infection with PVM in the mouse lung acquires increased significance. Further evidence that the inhibitory activity of Friedländer polysaccharide is not attributable to the molecular configurations which are responsible for specific serological reactions appeared when it was shown that oxidation with periodic acid abolishes immunological reactivity but does not diminish biological activity in infections with PVM.

Rigorous purification of polysaccharide preparations by a variety of procedures does not result in diminished inhibitory activity and has failed to provide evidence suggesting that some impurity other than the polysaccharide itself is the active substance[17]. Hydrolysis with either acid or alkali, if sufficiently prolonged, results in loss of all activity and dialysable fragments of the polysaccharide molecule, such as aldobionic acid, possess no activity.

Exceedingly small quantities of polysaccharide cause significant inhibition of multiplication of PVM. With Friedländer polysaccharide a single injection of no more than 2 micrograms per mouse is required. The degree of inhibition is not proportional to the amount of polysaccharide given; 6 micrograms usually causes inhibition of maximal extent and larger quantities do not yield significantly better results[29]. The lack of proportionality between quantity and effect suggests that a competitive mechanism is operative and raises the possibility that only a relatively small and fixed quantity of an essential cell substance is concerned with the effect. In terms of this hypothesis it would be assumed that the availability of such a substance is essential for the continued multiplication of the virus.

A puzzling fact, one which has not yet been explained satisfactorily, is the finding that, in infections with PVM in the mouse lung, polysaccharide exerts no inhibitory effect unless it is given intranasally. Even when as much as 1 milligram: 500 times the minimal effective intranasal dose, is given by any other route, there is no evidence of an inhibitory effect. It seems unlikely that the polysaccharide is destroyed by living mouse tissues inasmuch as it has been shown to remain present in apparently unaltered concentration in the mouse lung for more than one week[16]. However, that the polysaccharide may be disrupted by certain tissue constituents is suggested by the finding that there is in egg yolk a substance, presumably an enzyme, which destroys its biological activity[16].

As was pointed out earlier, if chemotherapeutic substances are to be effective in combatting natural viral infections, they should exert a beneficial effect upon the course of the disease when given well after evidences of infection have appeared. A desirable chemotherapeutic agent would be one which both stopped viral multiplication and also prevented the development of further pathological lesions. In experimental infections of the mouse lung with PVM, a single injection of Friedländer polysaccharide given as late as 4 days after inoculation of the virus causes significant inhibition of viral multiplication[20]. As might be expected, the earlier polysaccharide is given, the more marked the degree of inhibition. Perhaps of greater interest is the fact that administration of polysaccharide results in modification of the disease process in the mouse. Infections with PVM which are uniformly fatal in untreated animals are altered after polysaccharide is given and such treated animals recover. Moreover, as has been shown but recently[16], the normal course of the pneumonic

process induced by infection with the virus is changed and pulmonary consolidation does not progress and extend, as in the untreated mouse, after administration of polysaccharide. The results appear to simulate the normal recovery process which can be followed in animals inoculated with very small amounts of virus; in effect, the presence of Friedländer polysaccharide converts an overwhelming viral infection associated with maximal viral multiplication and resulting in death into a mild infection associated with markedly restricted viral multiplication which is followed by recovery. Such effects can be obtained if polysaccharide is given from a week before to 4 days after inoculation of PVM but are not evident if the substance is withheld and given only at still later stages in the experimental disease. After the 5th day of infection maximal viral multiplication has occurred and extensive pneumonia is already present. Polysaccharide given this late in the course of the disease has little, if any, effect upon the concentration of virus present in the lungs and does not significantly alter the existing pneumonic process. Inasmuch as polysaccharide shows no evidence of acting directly upon the virus *in vitro,* does not combine with it nor cause inactivation of the agent, it is not surprising that it is incapable of reducing the quantity of virus already present in infected tissue. That a substance with chemotherapeutic activity should fail to cause prompt reversal of a preexisting pathological lesion might be anticipated.

Among a number of viruses which have been studied in a similar manner with Friedländer and other bacterial polysaccharides, none has yielded analogous results, excepting only mumps virus[17]. Infections of mice or chick embryos with influenza A or influenza B virus are entirely unaffected by relatively large amounts of Friedländer polysaccharide as also are Newcastle disease virus infections of the embryo. Injection of polysaccharide some hours before any of these viruses is inoculated is also ineffective and no inhibition of viral multiplication is obtained. Thus, it appears there is striking specificity in the inhibitory effect of bacterial polysaccharides and those which are active with respect to PVM and mumps virus are inert relative to certain other viruses. Both in the mouse lung and in the chick embryo the viruses studied are thought to multiply within cells of identical type. Under these circumstances it is not possible to explain the selective inhibitory effect except in terms of the induction of a state of inutility of a cellular substance essential for the multiplication of some viruses but not for others. In the light of available evidence and the theoretical possibilities considered earlier, it appears probable that this substance is an intracellular component available in limited quantity and not essential for survival of the cell.

Mumps Virus. Infection of the chick embryo with mumps virus is affected by Friedländer polysaccharides in a manner closely similar to infection of the mouse lung with PVM[17]. The chief differences in the two viral infections are the lack of manifest disease and of definite pathological lesions with mumps virus in the embryo. This limits the study of the action of polysaccharide to its effect upon mumps virus multiplication.

When as little as 5 micrograms of polysaccharide per embryo is given, definite inhibition of mumps viral multiplication is obtained[17]. So far the capsular polysaccharides of Friedländer bacilli, types A, B, or C, are the only carbohydrates that have been found to possess this activity with mumps virus infections. A number of other

polysaccharides which show striking inhibitory activity in infections with PVM are entirely ineffective with mumps virus, additional evidence of the high degree of specificity of the effect. Inhibition of maximal extent may be obtained with 50 micrograms per embryo; larger quantities do not markedly increase the degree to which the infectious process is modified. As with PVM, the extent to which the multiplication of mumps virus is inhibited is not proportional to the amount of polysaccharide given[17]. As a consequence, it appears probable that, in this instance too, a competitive mechanism is operative and that only a limited quantity of some substance required by the virus is present in the embryo.

With mumps virus infections it is not essential that polysaccharide be given by the same route as the virus inoculum[17]. If polysaccharide is injected into the yolk sac and infection is established in the allantoic sac, inhibition of multiplication of the virus results. However, this does not occur unless the carbohydrate is transported in demonstrable amounts to the allantoic sac, as occurs in about 50% of instances. Mumps virus is not inactivated by polysaccharide nor does demonstrable combination between the two occur. Of more importance, the presence of large amounts of the substance in no way alters adsorption of the virus by susceptible cells; embryos treated with as much as 40 milligrams show normal adsorption of the agent and therefore it seems evident that the first step in viral multiplication is wholly unaffected[18].

As in the case of PVM, the effectiveness of the polysaccharide is independent of its immunological reactivity[17]. Oxidation with periodic acid does not diminish inhibitory activity but eliminates specific serological reactions; hydrolysis at pH 9.5 causes exactly opposite effects. Moreover, neutral mixtures of polysaccharide and homologous antibody show undiminished inhibitory effects of mumps virus infections[17]. It appears clear that the structural configurations which are responsible for the chemotherapeutic activity of the substance are different from those which characterize it as an antigen. So far, all efforts to identify the molecular structures of active polysaccharides which cause these biological effects have been fruitless.

A single injection of the substance given as late as 4 days after inoculation with mumps virus is effective in restricting viral multiplication. Similar to infections with PVM, more striking results are obtained if polysaccharide is given earlier. However, there is no significant difference in the effect obtained whether embryos receive the substance a few hours before, or as long as 48 hours after, infection is initiated[17]. Quantitative studies on mumps virus infection of the chick embryo indicate that all or nearly all susceptible cells are already infected by the 4th day. That inhibition of viral multiplication can be caused at this time is evidence in favor of the view that the effect is mediated by an intracellular constituent which is essential for viral synthesis. As would be expected from the fact that mumps virus is not inactivated by polysaccharide, there is no reduction in the concentration of preformed virus after injection of the substance. Modification of the infectious process appears to consist solely in the inhibition of further viral multiplication which, as was stated earlier, is formally analogous to the process of natural recovery.

Recent work[20] showed that all the individual particles in a population of mumps virus are not entirely identical. A very small proportion of the viral particles, about 1 in 10^4, are demonstrably different from the others and may be considered as naturally occur-

ring variants. These unusual particles are readily separated from the far larger number of typical viral particles because they are entirely resistant to the inhibitory effects of polysaccharide. When this is done, a resistant strain is obtained which multiplies in unrestricted manner in the presence of large amounts of the substance. So far as can be determined, except for this one property and in addition a slightly slower rate of multiplication, the resistant variant is in all other respects identical to the parent virus. It is evident that a viral variant resistant to the inhibitory effects of a chemical substance may be regarded as similar to a bacterial variant resistant to the action of a chemotherapeutic agent. There is, however, an essential difference. In the case of bacteria, chemotherapeutic agents are thought to exert their effects upon the bacterial cells themselves and variants are resistant because, by one means or another, they are capable of circumventing such action. With mumps virus the polysaccharide has, so far as can be determined, no action upon the virus *per se* but appears to act indirectly by competing with the virus for an intracellular constituent essential for multiplication of the agent. In these terms, the resistance of the variant virus would be explained on the basis that it does not require this constituent and therefore is capable of multiplication even though the host cell component is unavailable.

It was stated earlier that the finding of a chemical substance which would simulate the interference phenomenon might be a step toward eventual solution of the general problem of chemotherapy in viral infections. There are some provocative analogies between the effects of polysaccharide on infections with certain viruses and the capacities of the same agents to cause interference[19]. Ingenious experiments have made possible the demonstration that mumps virus interferes with the multiplication of PVM in the mouse lung[16]. Friedländer polysaccharide is an effective inhibitor relative to infections with either of these two agents but is wholly devoid of modifying action on infections induced with influenza viruses. Influenza A and B viruses show reciprocal interference[51] but neither one nor the other is capable of causing interference with PVM; similarly, both fail to interfere with the multiplication of mumps virus. Thus, it appears that there is complete correlation between the inhibitory activities of the polysaccharide and the results of interference experiments with these four viruses, which, it should be pointed out, are all immunologically unrelated. The two viral infections which are modified when polysaccharide is given do not show interference with the two which are unaffected by the same substance. These findings provide additional support for the concept that the synthetic mechanisms required by PVM and mumps virus are, in at least one point, closely similar if not actually identical and that those demanded of the cell by either influenza A or B virus are, with respect to the same point, different. It seems appropriate, as a working hypothesis, to raise the possibility that it is this critical point in the synthetic process which is blocked by polysaccharide. Chemotherapeutic activity in viral infections then would appear to result from induced alterations in metabolic mechanisms, as is the case too with bacterial infections. The basic difference lies in the point of attack; with bacteria the metabolism of the microorganism itself can be affected by available chemotherapeutic substances; with viruses it seems probable that success will be dependent upon the discovery of substances which affect the metabolism of the host cell.

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NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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ANTABUSE THERAPY IN CHRONIC ALCOHOLISM* †

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Two Danish physicians became ill at an evening party shortly after the cocktails had been served. Worst of all, they were the only guests that were made so. Making a simple epidemiologic study, they found the common factor to be the alcohol in the drink plus a new drug which the two had been taking to look for toxic effects. This substance, tetraethylthiuram-disulfide, had some beneficial action in scabies, and these Danes, Jacobsen and Hald[11], were investigating the possibility of using it as an anthelmintic. After this startling initial experience, they found that this ability of tetraethylthiuram disulfide to "sensitize" a person to the ingestion of alcohol was reproducible. They suggested it be given a trial in alcoholism. That was 2 years ago.

It appears that reactions of this nature have been known for some time in the rubber industry, but no reports appeared in the scientific literature. Similar substances are known for their chemical property to inhibit oxidation. Earlier work by Henzlik and Irvine[12] indicated this drug to be relatively non-toxic when taken internally. The pharmacological investigation of this substance by Asmussen, Hald, Larsen, and Jacobsen[1,2,10,12] revealed that, when taken alone, it has no or very slight effects on the human system but that following the ingestion of alcohol a very characteristic and subjectively uncomfortable reaction occurs. The work of Luban, Westerfeld[17], and Lutwak-Mann[18], on the metabolism of alcohol suggested the probability that tetraethylthiuram disulfide alters the oxidation of alcohol by the enzyme systems of the body. Westerfield *et al.*[23] showed that the first metabolite of alcohol was acetaldehyde, and Lutwak-Mann[17] demonstrated the presence of the alcohol dehydrogenase

* The Authors wish to express their thanks to Ayerst, McKenna and Harrison, Ltd., for the generous supply of "Antabuse" that has made our experience with this new drug possible.

† Having just learned that Antabuse will not be on general sale for another 12 months, we wish to pass this information on to our readers. EDITOR.

polysaccharides which show striking inhibitory activity in infections with PVM are entirely ineffective with mumps virus, additional evidence of the high degree of specificity of the effect. Inhibition of maximal extent may be obtained with 50 micrograms per embryo; larger quantities do not markedly increase the degree to which the infectious process is modified. As with PVM, the extent to which the multiplication of mumps virus is inhibited is not proportional to the amount of polysaccharide given[17]. As a consequence, it appears probable that, in this instance too, a competitive mechanism is operative and that only a limited quantity of some substance required by the virus is present in the embryo.

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Recent work[20] showed that all the individual particles in a population of mumps virus are not entirely identical. A very small proportion of the viral particles, about 1 in 10^4, are demonstrably different from the others and may be considered as naturally occur-

ring variants. These unusual particles are readily separated from the far larger number of typical viral particles because they are entirely resistant to the inhibitory effects of polysaccharide. When this is done, a resistant strain is obtained which multiplies in unrestricted manner in the presence of large amounts of the substance. So far as can be determined, except for this one property and in addition a slightly slower rate of multiplication, the resistant variant is in all other respects identical to the parent virus. It is evident that a viral variant resistant to the inhibitory effects of a chemical substance may be regarded as similar to a bacterial variant resistant to the action of a chemotherapeutic agent. There is, however, an essential difference. In the case of bacteria, chemotherapeutic agents are thought to exert their effects upon the bacterial cells themselves and variants are resistant because, by one means or another, they are capable of circumventing such action. With mumps virus the polysaccharide has, so far as can be determined, no action upon the virus *per se* but appears to act indirectly by competing with the virus for an intracellular constituent essential for multiplication of the agent. In these terms, the resistance of the variant virus would be explained on the basis that it does not require this constituent and therefore is capable of multiplication even though the host cell component is unavailable.

It was stated earlier that the finding of a chemical substance which would simulate the interference phenomenon might be a step toward eventual solution of the general problem of chemotherapy in viral infections. There are some provocative analogies between the effects of polysaccharide on infections with certain viruses and the capacities of the same agents to cause interference[19]. Ingenious experiments have made possible the demonstration that mumps virus interferes with the multiplication of PVM in the mouse lung[19]. Friedlander polysaccharide is an effective inhibitor relative to infections with either of these two agents but is wholly devoid of modifying action on infections induced with influenza viruses. Influenza A and B viruses show reciprocal interference[21] but neither one nor the other is capable of causing interference with PVM; similarly, both fail to interfere with the multiplication of mumps virus. Thus, it appears that there is complete correlation between the inhibitory activities of the polysaccharide and the results of interference experiments with these four viruses, which, it should be pointed out, are all immunologically unrelated. The two viral infections which are modified when polysaccharide is given do not show interference with the two which are unaffected by the same substance. These findings provide additional support for the concept that the synthetic mechanisms required by PVM and mumps virus are, in at least one point, closely similar if not actually identical and that those demanded of the cell by either influenza A or B virus are, with respect to the same point, different. It seems appropriate, as a working hypothesis, to raise the possibility that it is this critical point in the synthetic process which is blocked by polysaccharide. Chemotherapeutic activity in viral infections then would appear to result from induced alterations in metabolic mechanisms, as is the case too with bacterial infections. The basic difference lies in the point of attack; with bacteria the metabolism of the microorganism itself can be affected by available chemotherapeutic substances; with viruses it seems probable that success will be dependent upon the discovery of substances which affect the metabolism of the host cell.

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NEUROLOGY AND PSYCHIATRY

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ANTABUSE THERAPY IN CHRONIC ALCOHOLISM* †

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Two Danish physicians became ill at an evening party shortly after the cocktails had been served. Worst of all, they were the only guests that were made so. Making a simple epidemiologic study, they found the common factor to be the alcohol in the drink plus a new drug which the two had been taking to look for toxic effects. This substance, tetraethylthiuram-disulfide, had some beneficial action in scabies, and these Danes, Jacobsen and Hald[11], were investigating the possibility of using it as an anthelmintic. After this startling initial experience, they found that this ability of tetraethylthiuram disulfide to "sensitize" a person to the ingestion of alcohol was reproducible. They suggested it be given a trial in alcoholism. That was 2 years ago.

It appears that reactions of this nature have been known for some time in the rubber industry, but no reports appeared in the scientific literature. Similar substances are known for their chemical property to inhibit oxidation. Earlier work by Henzlik and Irvine[12] indicated this drug to be relatively non-toxic when taken internally. The pharmacological investigation of this substance by Asmussen, Hald, Larsen, and Jacobsen[1,2,10,12] revealed that, when taken alone, it has no or very slight effects on the human system but that following the ingestion of alcohol a very characteristic and subjectively uncomfortable reaction occurs. The work of Luban, Westerfeld[17], and Lutwak-Mann[18], on the metabolism of alcohol suggested the probability that tetraethylthiuram disulfide alters the oxidation of alcohol by the enzyme systems of the body. Westerfield *et al.*[23] showed that the first metabolite of alcohol was acetaldehyde, and Lutwak-Mann[17] demonstrated the presence of the alcohol dehydrogenase

* The Authors wish to express their thanks to Ayerst, McKenna and Harrison, Ltd., for the generous supply of "Antabuse" that has made our experience with this new drug possible.

† Having just learned that Antabuse will not be on general sale for another 12 months, we wish to pass this information on to our readers. EDITOR.

enzyme system leading to the formulation of acetaldehyde. When a subject who has been taking tetraethylthiuram disulfide, now with the proprietary name of Antabuse, takes a drink containing alcohol a sharp rise in the blood acetaldehyde level is demonstrable. When the proper dose of acetaldehyde is given intravenously the same signs and symptoms of the Antabuse-alcohol reaction appear. Consequently, evidence to date indicates that the toxic agent for the production of the Antabuse-alcohol reaction is an increase in the circulating acetaldehyde, an otherwise normal metabolite of alcohol. Indeed, the really chronic alcoholic seems to produce the fruity odor of acetaldehyde just as is so much more strongly observable during the Antabuse-alcohol reaction.

Absorption of Antabuse from the gastrointestinal tract is not complete. About one-fifth of the dose passes into the feces. However, the elimination is very slow. No Antabuse is excreted unaltered in the urine and indeed the sulfur-nitrogen ratio in the urine remains unchanged after taking Antabuse. Just what is the fate of Antabuse after absorption remains unknown. Due to the slow excretion, the effect of a single dose lasts a rather long time. A single dose of 1 gm. will produce a slight alcohol reaction 5 days later.

After these pharmacological and toxicological investigations, Hald, Jacobsen, and Martensen-Larsen[11,14,19] gave the drug an extensive clinical trial in Denmark in the treatment of chronic alcoholism, reporting favorable results in Lancet. In addition to the Danish medical journals, Dr. Glud[8] suggested its use in this country, and it has received some trial in Canada. The Canadian results have been reported by Bell and Smith[5], Ferguson[7], Gelbman and Epstein[8], and Jones[15]. These authors reported favorable results, but stressed the importance of caution. It was with this background that we decided to give this new therapy a trial at the Colorado Psychopathic Hospital.

Clinical Applications. When a patient has taken Antabuse in sufficient doses 12 hours to 3 days previously, the intake of alcohol results in the following symptoms: After 5 to 15 minutes, the person has a feeling of heat in the face. A few minutes later an intense vaso-dilatation is observed over the face and neck, making the whole area purple-red with an associated injection of the conjunctiva. At the same time the patient may complain of a throbbing headache or simply of a throbbing sensation in the head. The pulse rate is increased to 120 to 140 beats per minute, and the systolic and diastolic pressures show an initial moderate rise of 10 to 20 points which may be followed by a fall in blood pressure to the region of 80 over 20 mm. Hg. The extent of this fall is roughly related to the severity of the reaction. The respiratory rate increases, frequently with associated slight bronchial spasm, and the patient may complain of dyspnea. Higher doses of alcohol and Antabuse result in nausea, vomiting, pallor, a marked fall in blood pressure, bradycardia, coma, convulsions, and death.

These symptoms are accompanied by an intense feeling of discomfort in the patient who has a pulsating headache, palpitations, dyspnea, and general malaise followed by sleepiness. The discomfort is so intense that once experienced it prevents the majority of patients from further attempts to drink alcoholic beverages as long as they are taking Antabuse. As mentioned, the clinical effects of alcohol after the ingestion of Antabuse are due to the increased concentration of acetaldehyde in the blood. We, as

well as other authors before us, have duplicated these symptoms by the injection of appropriate amounts of acetaldehyde intravenously. (Blood acetaldehyde can be determined according to the method of Stotz[22].)

The character of the preliminary work-up and the subsequent follow-up has shown some variation in the reports in the literature. At present, we performed the preliminary psychiatric and physical examinations in the Colorado Psychopathic Hospital or in other hospitals, and also performed the test trials in the hospital. However, we are beginning to consider the problems of out-patient administration of this drug as reported by Gelbman and Epstein[8].

Acetaldehyde is a general body toxin, and for this reason the physical status of the patients selected for treatment with Antabuse must be carefully evaluated. General physical and neurological examinations are performed with a careful review for history of systemic disorders. The laboratory work includes an electroencephalogram, chest plate, electrocardiogram, kidney and liver function tests, occasionally a basal metabolic rate, and other studies as indicated to establish fully that the patient is in good physical health. At present, we feel that these studies should be negative in all respects. Furthermore, not only to further our research, but to gain a better understanding of the alcoholic patient, he receives a Rorschach, a Thematic Apperception, and a Wechsler-Bellevue test, and occasionally other psychological examinations. In addition, the patient gets a general psychiatric evaluation, and an evaluation as to the advisability of instituting regularly scheduled psychotherapeutic sessions. To date, we have made no attempt to screen or select our patients on the basis of the psychological and psychiatric examinations, but rather have placed the whole gamut of alcoholics, who measure up to the physical qualifications, on Antabuse so that we could learn more exactly what is the best selection; we hope to make an oral report on this before this review appears[4].

Jacobsen and Martensen-Larsen[14] suggested initial doses of around 1 to 2 gm. of Antabuse and reduction of dosage over a period of 3 days to a maintenance dose in the neighborhood of 0.5 gm. We have found that for routine use, 2 gm. on the 1st day, 1.5 gm. on the 2nd day, 1 gm. on the 3rd day, and 0.5 gm. on the 4th day, to be most satisfactory. On the 4th day the patient is given a test dose of his favorite alcoholic beverage to help us determine the proper dosage level of Antabuse and to give the patient an opportunity to experience the nature of the alcohol reaction. Depending upon the severity of this test reaction, the patient's dose of Antabuse is either increased, decreased, or continued the same for another 4 days, when he is given another test. Generally, we find 2 tests sufficient to adjust the maintenance dose and to give the patient an adequate experience. In our experience a reaction has reached the proper intensity when marked erythema of the face and neck with injection of the conjunctiva, a throbbing headache, slight dyspnea, occasional nausea and vomiting, and sleepiness have occurred. If the reaction is less intense than this, the Antabuse dose is increased to ¾ gm., or in some cases 1 gm. for 4 days before the next dose. If the reaction is more severe, characterized by a marked fall in the blood pressure, occasionally by bradycardia, lower abdominal cramps, and retching, the dose is diminished to ¼ gm. until the next test.

Obviously, in the process of these tests the patient has an experience similar to the conditioned reflex type of

therapy, and, indeed, we have had the occasional patient who complains of similar subjective symptoms when he smells alcoholic beverages; and 1 patient complained that some of the particularly realistic billboard advertising made him feel very uncomfortable. However, this conditioning effect is not the whole story. The beneficial results of Antabuse are on a psychological level differing from the conditioning experience. We will say something more about this later in this article.

Untoward Reactions. Marked to slight side effects have been reported, and we have noted also allergic dermatitis and urticaria following the administration of Antabuse. Generally, these allergic reactions can be well controlled with the simultaneous administration of one of the antihistaminics. One patient reported by Lewis and Bremers[16] was proven to have an allergy to the acetaldehyde alone. Various side effects to the Antabuse alone have been reported by some patients, including a metallic taste in the mouth, constipation, lassitude and inertia, and we have observed in about ¾ of the patients changes in the electroencephalogram which are probably related to the sedative effect experienced by the patients. This latter finding will be reported later[3]. In addition to these at present unimportant side effects, we have noted in the occasional patient a peculiar and unusually heightened sensitivity to alcohol while on Antabuse. During the test, the patient becomes extremely ill with much vomiting, precipitous fall in the blood pressure to as low as 50 over 0, pallor, labored respiration, and a very slow pulse. There seems to be no way of determining which patients are going to react in this fashion before the test. However, abnormalities of the electrocardiogram suggest that the patient's cardiovascular system may not be up to treatment with Antabuse. Jones[15] reported a like reaction which preceded the death of one of his patients.

A severe reaction can be, in some measure, controlled by the subcutaneous administration of ½ to 1 cc. of epinephrin 1:1000 to control the hypotension and bradycardia. Inhalations of 95% O_2 and 5% CO_2 will control the respiratory difficulties. Dr. McKeown[20] suggests the use of 1 gm. doses of ascorbic acid by mouth. The ascorbic acid may have a stimulating effect on the enzyme systems responsible for the oxidation of acetaldehyde. No specific antidote is known that will abort an unduly severe reaction.

It is this aspect of Antabuse therapy which limits its use and requires its administration in carefully controlled circumstances[6,7]. It is suggested that all patients on Antabuse carry a card to that effect with suggested measures for the control of the Antabuse-alcohol reaction.

Contrariwise, there are a few patients who show practically no response whatsoever to the alcohol tests even when they have been on doses as high as 1 gm. a day and 2 oz. of whiskey are taken. Consequently, it appears that some patients do not show heightened blood acetaldehyde levels following the test, or acetaldehyde is not particularly toxic to them. These patients are usually long standing alcoholics above 40 years of age. It is interesting to note that these patients who do not show a reaction to alcohol following the administration of the usual bar "shot" of whiskey are, on the whole, therapeutic failures. In addition to these untoward reactions, in the presence of other systemic diseases such as nephritis, cirrhosis, diabetes, epilepsy and the cardiovascular disorders very severe reactions to alcohol may occur. Several deaths have been reported in diabetics who have

been on Antabuse. At present selection on the basis of physical health is more important than selection on the basis of psychiatric status.

Psychiatric Implications. Initially, most of our patients expressed a great interest in this new therapy and readily cooperated. Only occasionally was it necessary for the physician in charge or for the family to encourage the patient to accept this treatment. Many patients voluntarily came to the hospital requesting this treatment after learning about it from other of our alcoholic patients, or after reading reports in the lay journals. Consequently, we had a group of patients to select from, who were ready and eager to start this therapy even though it was on an experimental basis. After the test trials the patients were discharged from the hospital and followed at 2-weekly intervals for 2 months and thereafter at monthly intervals. Generally we experienced no difficulty in getting the patients to continue to take their Antabuse. The Danish authors[14] suggested that it might be well for the marital partner, or other person in the family, to take the responsibility of seeing that the patient took his Antabuse tablet each day. We have not found this to be as efficacious as having the patient himself assume the responsibility. Most patients take the medication regularly for a period approximating 3 months, and thereafter they frequently desire to stop. This wish, when expressed in the follow-up visits, is honored, but we give him a small quantity of the drug to take when he feels the pressure for a drink coming on; and he is encouraged to return any time he so desires. We have had patients who have stopped taking Antabuse and have resumed drinking who later voluntarily returned to be re-started on Antabuse.

It seems then that the patient welcomes the opportunity to take Antabuse and many desire to continue as long as alcoholism is a problem. In the course of the follow-up interviews it becomes apparent that the taking of Antabuse has considerable symbolic significance. The taking of medicine regularly is definitive evidence to the patient, to the patient's family, and to their friends that the patient is ill, that he has been to see a doctor about this illness, and a remedy has been prescribed. In situations of pressure, where otherwise the alcoholic might be induced to drink excessively or chronically, he refrains from doing so; not so much because it would make him ill, but because alcoholism itself is an illness which the patient is able to recognize, and for which he is taking medicine and receiving treatment. One patient takes his pill with him in his lunch pail. After lunch he takes the Antabuse. Doing so, with an explanation to his fellow workers, is sufficient to give him an acceptable excuse for not joining them in their usual round of beers after work.

What in effect amounts to the forceable withdrawal of alcohol, in some instances, results in heightened anxiety and tension in the patient with difficulty in handling the everyday problems of emotional significance. Sometimes psychotherapy on a regular weekly basis for a period of 4 to 6 weeks has enabled the patient to deal successfully, in psychotherapy, with these conflictual problems and arrive at some solution, other than drinking. True, these solutions may be equally neurotic; but on the other hand they are usually more socially acceptable and do not interfere with the patient's economic life to the extent that does chronic alcoholism. However, the effectiveness of psychotherapy following the starting of Antabuse varies a great deal with the personality structure of the patient. These variations will be re-

ported later[4]. Some patients do remarkably well with Antabuse alone and with little of what could be termed formalized psychotherapy, while others are complete failures even with the most carefully performed psychotherapeutic follow-up. It appears that this difference is more a difference in the personality structure of the patient than in the method. The Alcoholics Anonymous group provides support of a therapeutic nature and if our patients are not already members, they are encouraged to join.

better, 12 somewhat better and 16 unchanged. After a short follow-up, Gelbman and Epstein[8] report that out of 55 cases, 45 had not at that time reverted to their drinking habits and 10 were classified as failures. Table 1 gives a summary of some of the results reported in the literature, including our results to date.

It is hard to say what one means by "recovered," "much better," or "failure." In some instances the family may think the treatment is immensely successful, while the physician would be prone to

TABLE 1.—THE RESULTS OF ANTABUSE IN THE TREATMENT OF ALCOHOLISM REPORTED TO DATE IN THE LITERATURE

Author	*Follow-up duration (months)*	*Number of cases*	*"Recovered"*	*"Somewhat better"*	*"No change"*	*Lost contact*
1. Martensen-Larsen[13]	7	25	14	8	3	
	4	27	21	1	5	
	2	31	26	4	1	
2. Jacobsen and Martensen-Larsen[14]	6	104	52	31	16	5
	9	42	22	9	11	
3. Gelbman and Epstein[8]	6	55	45		8	2
4. Peterson *et al.*[21]	6	50	38	5	2	5
5. Dale and Ebaugh (herewith reported)	6	29	9	12	5	3
* Totals (6 month follow-up)		238	144	48	31	15

* In arriving at the totals it is assumed that the total cases of Jacobsen and Martensen-Larsen is 104. Thus, Item 2 is totaled with Items 3, 4, and 5 and the other follow-up periods of Martensen-Larsen are excluded from the total.

Both the Danish and Canadian workers have stressed the importance of psychotherapy; and Jacobsen and Martensen-Larsen[14] have successfully used group therapy which seems like a good idea to us.

The Effectiveness of Antabuse Therapy. At present a statistical analysis of the effectiveness of Antabuse therapy would be misleading. The duration of all studies to date is too short when measured in terms of a chronic, relapsing disease like alcoholism. Jacobsen and Martensen-Larsen[14] in a 6 month report of their patients in Denmark report that of 99 patients, 52 were socially recovered, 19 were much

call it a failure. One wife expressed boundless gratitude that her husband had stayed sober for 6 weeks, even though he had already fallen off the wagon. However, 6 weeks was the longest sober period that she could remember for some years and this gave her new hope. For statistical purposes this patient would probably be listed as a failure; but the family did not consider it in that light at all.

At present, the experience with Antabuse is of short duration and the total series small. The published reports stress caution especially in regard to the possibility of toxicity of the Antabuse itself and the severity of the

Antabuse-alcohol reaction. The general tone of these preliminary reports indicate that Antabuse will probably have a place among other measures in the treatment of chronic alcoholism.

Summary. Tetraethylthiuram disulfide, Antabuse, in the last two years has received considerable attention concerning the possibility of its use in the treatment of chronic alcoholism. It was discovered only 2 years ago that, by itself, Antabuse was a relatively non-toxic substance, but when alcohol is consumed in addition to the Antabuse, a very pronounced reaction occurs which is disagreeable to the patient. Generally, a patient who has been taking Antabuse regularly is prohibited from drinking because if he does so he will become so violently ill he will be unable to continue, and thus the sequence from the first drink to chronic drinking is broken.

Investigation to date seems to indicate that the Antabuse in some way influences the normal metabolism of alcohol resulting in the formation of high blood levels of acetaldehyde; and it is the acetaldehyde which accounts for the toxic symptoms. Few untoward reactions to Antabuse alone have occurred, although several deaths during the course of an Antabuse-alcohol reaction have been reported.

The clinical experience with this drug is short. There is a group of about 20% who are utter failures, another group of about 20% who seem to do very well, with all variations between. It appears that the psychological effects of taking a pill to prevent drinking have equal importance with the physiologic effects. The techniques and methods of psychotherapy to run conjointly with the administration of Antabuse need further investigation.

Antabuse will probably take its place among other measures for the therapeutic approach to the alcoholic problem; and only further clinical trial can establish its uses and limitations.

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PROCEEDINGS OF

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On the Toxicity and Toxicology of Surface-active Agents. HEINRICH BRIEGER, M.D. (Dept. of Prev. Med., Jefferson Med. Coll., Phila.). Effects of nonpolar-polar organic ions on isolated biologic material have been investigated for years. The widespread use of surface-active agents has stimulated the study of their toxicity in the living organism.

Intestinal *absorption* has been shown for few compounds or groups. Absorption of polyethylene glycols decreases with increased molecular weight. Skin absorption has been proven only in isolated animal experiments. Urinary *excretion* of intravenously injected polyethylene glycol 400 is incomplete in human beings and rabbits. Sorbitan laurate, stearates, oleates (SPANS) are split up in the digestive tract similarly to edible fats and oils. Polyoxyethylene sorbitan laurate, stearates, oleates (TWEENS) are hydrolyzed in the presence of lipase; the polyoxyethylene polyol and the hexitol anhydride hydrolysates are excreted unchanged. The *toxicity* of surface-active agents is of a low order. Anionic or non-ionic compounds are either slightly toxic or practically non-toxic, according to the single dose oral toxicity test (LD 50). Very large doses produce parenchymatous degeneration and necrosis of intestinal mucous surfaces. The toxicity of cationic agents is higher, but no LD 50 was lower than 230 mg. per kg. Long-extended feeding of undiluted ionic agents, especially of quaternary ammonium salts, causes intestinal irritation and inanition in some species. Non-ionic compounds as used in foods are practically non-toxic.

Nonpolar-polar organic ions precipitate or denature *enzymes* or form complexes with enzyme proteins. *In vitro* experiments with a great number of agents confirm this observation; there is occasionally a stimulating effect. However, non-ionic agents, too, interact with digestive enzymes. A correlation between this effect and depression of interfacial tension was not apparent. Results obtained *in vivo* are not conclusive. The *hemolytic activity* of surface-active agents *in vitro* differs widely and is only within narrow limits correlated with chain length or surface activity. Some non-ionic compounds are non-hemolytic but seem to change the erythrocytic structure. Plasma and, in some instances, cholesterol counteract hemolysis. Hemolysis is inhibited *in vivo*.

Infra-red Spectra of Frozen Tissue Sections. H. P. SCHWARZ, M.D., H. E. RIGGS, M.D., C. GLICK, Ph.D., W. CAMERON, E. BEYER, B. JAFFE, and L. TROMBETTA (Diabetic Coma Project and Div. of Neuro-path., Philadelphia Gen. Hosp.). After killing of the rabbits used in this study, the organs were rapidly frozen with CO_2. Frozen sections of 25 to 50 microns thickness obtained with the technique of Adamstone and Taylor were placed on silver chloride plates and dried at low temperature. For recording of the spectra with the Beckman IR2, the desired part of the section was exactly centered and covered with a specially designed

mask so that no infra red energy would pass through any area of the plate not covered by the tissue section. Blanks were recorded using the masks with the same surface and same slit widths. Proper corrections for different amplifications were applied.

Spectra of liver, heart, kidney cortex and medulla, adrenal thymus, spleen, lymph node, muscle, sciatic nerve, grey and white matter of the brain were recorded from 14 to 2.8 microns, showing the known bands of protein vibrations below 8 microns and a finger print region between about 10.30 and 8 microns. A band of medium to weak strength almost always exactly located at 10.30 $\pm$.03 microns was seen in all the tissue sections with the exception of the liver sections of our rabbits which did not receive insulin. Although the 10.30 band was regularly seen after insulin, no conclusion should be drawn from these differences between the insulin animals and the control animals at present. Coccidiosis frequently found in rabbits may have caused liver damage.

The fact that we found at 10.28 to 10.30 microns the strongest band in thymus nucleic acid (Bios) and at 10.23 in adenosine, that Randall *et al.* recorded a weaker band at 10.26 in adenine sulfate, and the absence of this band in hypoxanthine (own data) and in uric acid and guanine (Randall *et al.*) may be significant for the assignment of the vibration. In the other part of the finger print region (*e.g.* between 9.89 and 8 microns) significant differences of the spectra of the tissues from different organs are apparent. One and the same organ, however, invariably shows a similar spectral pattern. Different parts of the brain and sciatic nerve tissue show a strong band at 9.35 $\pm$.03 microns. Although more or less strong bands can be found in nucleic acid and, or, nucleosides at this wave length, further studies with infra red and Raman spectra are necessary.

In the brain and sciatic nerve tissue, these bands at 10.30 $\pm$.02 and 9.35 $\pm$.03 microns completely disappeared after extraction with a mixture of ether and chloroform. The band at 6.44 $\pm$.01 microns corresponding to the deformation vibration of NH contained in proteins and polypeptides, however, was not influenced by the extraction. It was decided, therefore, to use that 6.44 micron band as internal standard for quantitative estimations of the concentration of those structures which produce the spectra at 10.30 $\pm$.02 and at 9.35 $\pm$.03 in the brain. It was assumed that the relation of optical densities $\frac{D10.30}{D\ 6.44}$ called K_1 and $\frac{D9.35}{D6.44}$ to be referred to as K_2 were independent of thickness of the sections and the "protein background" and that they are a true expression of the concentration and molecular extinction of the structures causing the vibrations at 10.30 or 9.35. The correctness of these assumptions was proved in sections of the same tissue and different thickness (25 and 50 microns) and some duplicates of the same tissue which gave almost identical K_1 and, or, K_2 values.

In a large number of sections through different parts of the normal brain, the K_1 values vary from .194 to .440 and the K_2 values vary from .480 to .832. This shows a larger variation than would actually exist if the same parts of the brain (*e.g.* frontal cortex, hippocampus, basal ganglia, tectum, and cerebellum) were compared with one another. In animals killed in insulin shock after convulsions, changes of the K_1 and, or, K_2 figure are noticeable. In the hippocampus K_1 figures of 0 and .130 and K_2 figures of .456 and .376 and one high K_2 of .931 were found. The changes occurred in 3 out of 5 shock experiments. In the basal ganglia sections of one experiment, the

K_1 was absent and the K_2 was absent and, or, greatly decreased in one section while the K_2 rose to .929 in another section. In the tectum area the K_2 was decreased to .439 in one experiment. In the cerebellum one low K_2 of .431 was noted. One study in an animal which did not develop shock after insulin injection showed normal K_1 and K_2 figures in different parts of the brain. More experiments in different species are contemplated before conclusions for men are drawn.

The Effects of an Anoxia Test on the Coronary Circulation and Cardiac Dynamics of the Anesthetized Dog. E. L. Foltz, M.D., R. G. Page, M.D., W. F. Sheldon, M.D., H. Wendel, M.D., and J. J. Saÿen, M.D. (Edward B. Robinette Foundation, Hosp. of the Univ. of Penna., and the Depts. of Pharmacology and Pathology, Sch. of Med., Univ. of Penna.). The effects of anoxia on the coronary circulation and cardiac dynamics were studied in 10 normal, intact, anesthetized dogs by catheterization procedures and the application of the nitrous oxide method of measuring blood flow. Variation in the levels of arterial O_2 saturation was noted after exposure of the animals to 8% and 10% O_2 mixtures in N_2; the level of arterial O_2 saturation was therefore used to classify the responses observed.

With arterial O_2 saturation levels between 60 to 69%, the mean coronary blood flow increased 100% over control levels; this change occurred with a mean increase in cardiac O_2 consumption of 50%. When arterial O_2 saturation dropped to 40 to 49%, the mean coronary flow increased approximately 200% over control levels while the cardiac O_2 consumption increased to a level about 75% above control values.

These changes occurred when cardiac work was increased chiefly through a rise in mean arterial blood pressure. A consistent increase in pulse rate was noted, but this rise was not sufficient to be considered as significant in this small series.

Coronary resistance (mean arterial B. P. per coronary flow) fell considerably as the coronary arterio-venous O_2 difference increased. In spite of a lowered coronary resistance and an increased blood flow, the coronary venous O_2 saturation fell from 30 to 16%; this we interpreted as a reflection of myocardial anoxia which occurred in spite of an active coronary vasodilatation.

Measurement of Alveolar Ventilatory Components. W. S. Fowler, M.D., E. R. Cornish, Jr., M.D., and S. S. Kety, M.D. (Dept. of Physiology and Pharmacology, Grad. Sch. of Med., Univ. of Penna.). Several investigators have presented the exponential equation describing the time course of pulmonary N_2 elimination during the inhalation of O_2, assuming uniform pulmonary ventilation. Continuous and simultaneous measurements of expiratory volume flow and N_2 concentration of respired gases (Lilly-Hervey N_2 meter) during the first several minutes of O_2 inhalation showed that uneven pulmonary ventilation exists and causes difficulties in the use of this equation especially in patients with chronic pulmonary disease but also in healthy persons. The N_2 concentration of alveolar gas expired after O_2 inhalation varies even during one exhalation, precluding use of directly measured alveolar N_2 concentrations; also the N_2 curves of some healthy persons and many patients with pulmonary disease could not be described by this equation. These difficulties were overcome by 1, obtaining the mean total expired N_2 concentration from the simultaneous N_2 and flow records; this has only one value for any single expiration; 2, developing an additional equation for a 2-phase system having one total tidal volume, the mean expired N_2 concentration of which is a function of both

ventilating phases. Measurement of tidal volume, number of breaths and mean expired N_2 concentration are required. Solution of the equation gives values for lung volume (functional residual capacity) and effective tidal volume (tidal minus dead space) for each phase.

Experiments with 1 bellows, or 2 bellows ventilated synchronously at different rates, gave data which, on solution by the one or 2-phase equations, agreed with the known volumes. The records of certain persons can be described by the equation for a single ventilatory phase. In others, the 2-phase equation is necessary; in pulmonary emphysema there appears to be marked hyperventilation of a small, and hypoventilation of a large lung volume.

Evidence that Alloxan is Converted to Alloxanic Acid in Blood. D. Seligson, M.D., H. Seligson, and R. Keisman (George S. Cox Medical Research Institute, Univ. of Penna.). As the first part of a study to investigate any possible relationship between alloxan diabetes and diabetes mellitus, the chemistry of alloxan decomposition in plasma is reported. Others have demonstrated the instability of alloxan in blood and the conversion of alloxan to alloxanic acid in alkaline solutions. The following procedures were used to study the nature of this decomposition: 1, Ceric Sulfate does not oxidize alloxan but it does oxidize alloxanic acid stoichiometrically under controlled conditions. This reaction may be used to follow the conversion of alloxanic acid by measuring ceric sulfate consumed or CO_2 liberated. 2, Alloxan and alloxanic acid are hydrolyzed stoichiometrically in hot alkali to salts of oxomalonic acid (mesoxalic) for which colorimetric, titrimetric and gasometric analyses have been developed. 3, Isolation procedures for alloxanic and oxomalonic acids using paper chromatography and ion exchange have afforded means of identifying the conversion product of alloxan in plasma. Kinetic studies revealed that alloxan in neutral buffers is converted completely to alloxanic acid; the decomposition is a first-order reaction with alloxan having a half-life of 2 to 3 minutes at room temperature. The same appears to be true of alloxan added to plasma. The reaction is at least 90% complete in plasma exposed to air. The presence of borate ions accelerates the reaction about 20 times, a fact which can explain the preventive action of boric acid in alloxan diabetes. The major end-product formed when alloxan is added to plasma exposed to air is alloxanic acid and not dialuric acid as has been implied in the literature.

BOOK REVIEWS AND NOTICES

OCCUPATIONAL EYE DISEASES AND INJURIES. By JOSEPH MINTON' F.R.C.S. (Eng.), Hunterian Prof., Royal Coll. of Surgeons. Pp. 184; 24 ills. New York: Grune & Stratton, 1949. Price, $4.50.

THIS is a short account of the eye industrial hazards in England. In the majority of instances the type of industrial accident seen in England is the same as that in America, and although percentages may be different in the two countries, the over-all picture will be the same. Some industries, on the other hand, are so differently pursued in the two countries that much of the Author's experience will not be found applicable to conditions in this country—for example, in coal mining and glass blowing. The standards of vision are somewhat different in this country than in England. On the whole, however, the book is useful for anyone interested in the subject. F. A.

HISTOLOGY. By ARTHUR WORTH HAM, M.B., Prof. of Anatomy, Univ. of Toronto. Pp. 756; 445 ills., 4 in color. Phila.: J. B. Lippincott, 1950. Price, $10.00.

THIS new and worthwhile book is written by an eminent histologist who spent some years teaching pathology. His broad training is reflected in the text, which stresses the relation of histology to physiology and to pathology. Thus there are excellent and well illustrated accounts of repair of fractures, of burns and skin grafting, of edema, of inflammation, of the disturbances of various endocrine glands, and of similar subjects not usually covered in texts of histology. Throughout the book it is made clear that the student of histology must learn to think in three dimensions, that is to say he must learn to "translate" the thin and practically two-dimensional microscopic preparations he sees into three-dimensional structures. This is not an easy task, and not the least merit of the text are the descriptive and pictorial aids which will help the student in acquiring the art of making mental reconstructions.

The book is readable, and over 90% of the many illustrations are new or original. The Reviewer warmly recommends this book, not only to students of histology and of pathology but also to graduates who feel the need of acquiring a broader background in an important medical discipline; he completely agrees with the Author's statement in the concluding paragraph of the preface: "I should like to remind the reader that, since the time of Virchow, histology has been the chief basis in reality for our concepts of normal and disease processes. With modern medicine becoming more complex every day, this is a very imperative function for histology to perform, and its contemplation leads to the conclusion that present day students should be learning more rather than less histology." B.L.

BRING OUT YOUR DEAD. By J. H. POWELL. Pp. 304; 5 ills. Phila.: Univ. of Penna. Press, 1949. Price, $3.75.

VIEWED with a hindsight based on knowledge of the mosquito transmission of yellow fever, the story of Philadelphia's epidemic derives a special interest from its account of a number of observations that brushed closely by significant truths yet were lost in the maze of fantastic beliefs and theories. We read of wind from the agricultural north being associated with fewer cases; wind from the swampy southern districts multiplying cases; the relative immunity of negroes and the exiles from the West Indies; the greater incidence of cases in the crowded alleys than in the houses on wide airy streets; the unusual frequency of mosquitoes; "few who went gunning in the fields and marshes escaped the infection."

The medical profession does not emerge from the catastrophe unscathed. To be sure, some remained and worked courageously and some of them made careful observations in the face of great obstacles. Others "nobly striving, nobly fell." Also the fantastic and uncontrolled theories were characteristic of 18th century medicine. However, many fled the city in spite of their special obligations to the public, "finding matters of private concern that required them to be absent." All honor, then, to the "incredible" Benjamin Rush and the faithful few who stayed and frequently died at their posts. Likewise to the conscientious and able Major Clarkson, to Peter Helm and Stephen Girard, who brought efficient order and hope for those in the temporary hospital at Bush Hill, and to the two negroes who led the African Society in volunteering the aid that so many whites feared to give.

The Author, a well known writer on historical subjects, makes the odd statement:

"Had I more time and ability, I should have made this book a novel." Fortunately, he comes up with something better—a tale that combines a vivid picture of human values with an accurate account of a terrifying plague, and one that is based on original sources that are noted in an addendum.

To the extensive literature on the 1793 epidemic that already exists, Mr. Powell's book is a valuable addition. E. K.

POSTGRADUATE GASTROENTEROLOGY. Edited by HENRY L. BOCKUS, M.D., Prof. of Gastroenterology, Univ. of Penna. Graduate School of Med. Pp. 670; 258 ills. Phila.: W. B. Saunders, 1950. Price, $10.00.

THE eminent 40 or more "Members of the (?) Faculty and Contributors" are listed by name just before the Preface, but as the subject covered by each one is not added, it is impossible to determine what each has contributed short of fingering through each of the 640 pages. The book loses correspondingly in value. Much space is consumed by "Questions and Answers" and the presentation of cases. The vogue for this kind of presentation in current medical books will doubtless help to surmount what seems like an exceedingly high price.

As usual with Saunders publications, the book is well turned out. E. K.

NEW BOOKS

Structure in Relation to Cellular Function. By ROBERT CHAMBERS, *et al.* Annals of the N. Y. Academy of Sciences, **50**. Pp. 815-1012. New York: The Academy, 1950. Price, $3.00.

Proceedings of the 1st Annual Symposium on Orthopedic Appliances. Edited by A. S. GLUSHIEN, M.D., *et al.* Pp. 307; illustrated. Washington, D. C.: Orthopedic Appliance and Limb Mfg. Assoc. Price, $5.00.

Endodontia. By BERNHARD GOTTLIEB, M.D., SETH LEE BARRON, D.D.S., and J. HOBSON CROOK, D.D.S., Baylor Univ., Dallas, Texas. Pp. 177; 103 ills. St. Louis: C. V. Mosby, 1950. Price, $6.00.

THE contributions of Gottlieb and his original coworkers have been particularly noteworthy in the field of experimental pathology. Much of this work has been reviewed in this book and its bearing on the problem of root canal treatment for human patients elucidated. Gottlieb's point of view is always stimulating and original. His book will certainly be widely read, and those who disagree with parts of it will undoubtedly publish further data to establish their particular points of view. Since this subject forms the basis of much of the so-called focal infection theory of disease, contributions on the basis of wide clinical experience supplemented by extensive animal experimentation are of great value. It is unfortunate that detailed steps of procedure are scattered throughout the volume and are not given in outline form. P. B.

Menstruation and Its Disorders. Edited by EARL T. ENGLE. Pp. 350; 105 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $6.50.

THIS record of the Proceedings of the Conference on Menstruation presented by the National Committee of Maternal Health consists of 13 presentations by outstanding leaders in the study of normal and abnormal physiology of the menstrual cycle. It is particularly refreshing to note that basic physiologic studies are presented with some reference to clinical applicability. Of special note is the paper by C. L. Buxton on the atypical secretory phase of the menstrual cycle with an excellent correlation of clinical studies relating to some of the hitherto unexplained abnormalities of the menstrual cycle.

This book will be of value to the endocrinologist and to obstetricians and gynecologists interested in the problem of infertility. G. W.

Physiology of the Eye. Vol. 1. *Optics.* By ARTHUR LINKSZ, M.D., New York Univ. College of Medicine. Pp. 334; 137 figs. New York: Grune & Stratton, 1950. Price, $7.50.

THIS is a well written, easily understandable text, beautifully illustrated with diagrams. The Author talks as if to students in an informal way, and the text continually reminds the reader that he is being indoctrinated in a painless manner to what is often a disagreeable subject. Most books upon optics are written by people with mathematical minds; here the subject is approached from a visual rather than an abstract angle. It can be recommended to those wishing information on the eye as an optical instrument. F. A.

Clinical Electroencephalography. By ROBERT COHN, M.D., Director of Neurological Research, U. S. Naval Hosp., Bethesda, Md. Pp. 639. New York: McGraw-Hill, 1949. Price, $14.00.

"THIS work is a compilation of data obtained from . . . 10,000 patients over a 12-year period . . . The text is so developed that the EEG interpretation follows directly from the basic physical description of the recorded wave forms." The Author, who has had rich training in bioelectric phenomena and is a Diplomate of the American Board of Neurology and Psychiatry, should be well qualified to write this timely book.

Angiology. Edited by SAUL S. SAMUELS. Vol. 1, No. 1, February, 1950. Pp. 107. Balt.: Williams & Wilkins, 1950. Price, $1.50 ($8.00 a year).

THIS new journal, signalizing that "a new specialty has come of age", hopes to cover the latest advances in this important field and to be aided thereto by the Research Foundation that its Board has founded.

Thrombosis in Arteriosclerosis of the Lower Extremities. By EDWARD A. EDWARDS, M.D., Clinical Assoc. in Anatomy, Harvard Med. School. Pp. 74; 33 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.00.

Multiple Sclerosis and the Demyelinating Diseases. Edited by WOLTMAN, H. W., *et al.* Proc. Ass'n Res. in Nerv. and Mental Dis., Vol. 28. Pp. 675; 153 ills. Balt.: Williams & Wilkins, 1950. Price, $12.00.

Water and Salt Depletion. By H. L. MARRIOTT, M.D., Middlesex Hospital, London. Pp. 80; 10 figs. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.00.

Transactions of the American Goiter Association. Annual Session, May 26-28, 1949. Pp. 460; illustrated. Springfield, Ill.: Charles C Thomas, 1950. Price, $10.50.

B.C.G. Vaccination in Theory and Practice. By K. NEVILLE IRVINE, D.M., M.A., B.Ch. Oxon. Pp. 130. Springfield, Ill.: Charles C Thomas, 1950. Price, $3.00.

Quinidine in Disorders of the Heart. By HARRY GOLD, M.D., Prof. of Clinical Pharmacology, Cornell. Pp. 115. New York: P. B. Hoeber, 1950. Price, $2.00.

THIS is an excellent little monograph on the clinical pharmacology of quinidine. It summarizes in an inclusive fashion Dr. Gold's experience with the indications and contraindications for the use of this drug. The concise discussions of dosage and routes of administration make it of practical value to both the medical student and the practicing physician. W. J.

NEW EDITIONS

Penicillin, Its Practical Application. Edited by SIR ALEXANDER FLEMING, Univ. of London. 2d ed. Pp. 491; 63 ills. St. Louis: C. V. Mosby, 1950. Price, $7.00.

THIS 2d edition has been rewritten and enlarged by its famous editor and 32 collaborators. The practical use of penicillin in the treatment of a wide variety of clinical infections is discussed in a delightfully concise manner. Comparisons are frequently made with other types of therapy. In preliminary chapters, the history, chemistry, pharmacology and methods of administration of penicillin as well as the bacteriological control of penicillin therapy are presented. H. Z.

Urological Surgery. By AUSTIN INGRAM DODSON, M.D., Prof. of Urology, Med. Coll. of Virginia. 2d ed. Pp. 855; 645 ills. St. Louis: C. V. Mosby, 1950. Price, $13.50.

THE 1st edition (reviewed in this journal, **208**, 814, 1944) has here been enlarged by some 90 pages and 70 illustrations, and the contributing authorities are increased from 7 to 12. Text, type and illustrations are clear, and this edition should be even more useful than its predecessor to urologists, general surgeons, medical students and general practitioners.

Community Health Organization. By IRA V. HISCOCK, M.P.H., Sc.D., Yale University. 4th ed. Pp. 278. New York: Commonwealth Fund, 1950. Price, $2.75.

THIS revised edition brings up to date a book that has been widely used in the past for concise information on community health service. It covers all angles of community health organization from general planning to the various specialized services and a discussion of finances. In an era when everyone is health conscious, this book is a most valuable guide for either lay or medical groups. H. V.

Textbook of Bacteriology. By JOSEPH M. DOUGHERTY, PH.D., and ANTHONY J. LAMBERTI, M.S., Villanova College. 2d ed. Pp. 491; 141 ills. St. Louis: C. V. Mosby, 1950. Price, $5.75.

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